CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074163

Trade Name : NAPROXEN TABLETS

Generic Name: Naproxen Tablets 250mg, 375mg and 500mg

Sponsor : Danbury Pharmacal, Inc

Approval Date: February 10, 1995

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074163

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074163

APPROVAL LETTER

DIV

ANDA 74-163

FEB 10 1995

Danbury Pharmacal, Inc.
Attention: Edward M. Cohen, Ph.D.
131 West Street
Danbury, CT 06810

Dear Sir:

This is in reference to your abbreviated new drug application dated December 31, 1991, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Naproxen Tablets USP, 250 mg, 375 mg, and 500 mg.

Reference is also made to your amendments dated March 13, 1992, and April 12, July 27, August 26, and December 20, 1993 and February 1 and 6, 1994.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your 250 mg, 375 mg, and 500 mg tablets to be bioequivalent to those of the listed drug (Naprosyn Tablets 250 mg, 375 mg and 500 mg, respectively, of Syntex Laboratories, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074163

FINAL PRINTED LABELING

Each tablet contains:
Naproxen, USP ..... 500 mg

Store at controlled room temperature, 15°-30°C (59°-86°F).

N 3 0591-5818-04 8

DANBURY
PHARMACAL, INC.
DANBURY, CT 06810

NDC 0591-5818-04

NAPROXEN TABLETS, USP

500 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 TABLETS

USUAL DOSAGE: See package insert for dosage and full prescribing information.

Dispense in a well-closed, light-resistant container as defined in the USP, with a child-resistant closure.

A-A

Control No. and Exp. Date

LABEL
SAMPLE

Each tablet contains:
Naproxen, USP ..... 500 mg

Store at controlled room temperature, 15°-30°C (59°-86°F).

N 3 0591-5818-04 8

DANBURY
PHARMACAL, INC.
DANBURY, CT 06810

NDC 0591-5818-04

NAPROXEN TABLETS, USP

500 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 TABLETS

USUAL DOSAGE: See package insert for dosage and full prescribing information.

Dispense in a well-closed, light-resistant container as defined in the USP, with a child-resistant closure.

A-A

Control No. and Exp. Date

LABEL
SAMPLE

Each tablet contains:
Naproxen, USP ..... 500 mg

Store at controlled room temperature, 15°-30°C (59°-86°F).

N 3 0591-5818-03 1

DANBURY
PHARMACAL, INC.
DANBURY, CT 06810

NDC 0591-5818-03

NAPROXEN TABLETS, USP

500 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 TABLETS

USUAL DOSAGE: See package insert for dosage and full prescribing information.

Dispense in a well-closed, light-resistant container as defined in the USP, with a child-resistant closure.

A-A

Control No. and Exp. Date

LABEL SAMPLE

Each tablet contains:
Naproxen, USP ..... 500 mg

Store at controlled room temperature, 15°-30°C (59°-86°F).

N 3 0591-5818-03 1

DANBURY
PHARMACAL, INC.
DANBURY, CT 06810

NDC 0591-5818-03

NAPROXEN TABLETS, USP

500 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 TABLETS

USUAL DOSAGE: See package insert for dosage and full prescribing information.

Dispense in a well-closed, light-resistant container as defined in the USP, with a child-resistant closure.

A-A

Control No. and Exp. Date

LABEL SAMPLE

FEB 10 1995

Each tablet contains:
Naproxen, USP ..... 500 mg

Store at controlled room temperature,
15°-30°C (59°-86°F).

N
3 0591-5818-02 4

DANBURY
PHARMACAL, INC.
DANBURY, CT 06810

NDC 0591-5818-02

NAPROXEN TABLETS, USP

500 mg

CAUTION: Federal law prohibits dispensing without prescription.

250 TABLETS

USUAL DOSAGE: See package insert for dosage and full prescribing information.

Dispense in a well-closed, light-resistant container as defined in the USP, with a child-resistant closure.

A-A

Control No. and Exp. Date

FEB 10 1995

APPROVED

LABEL
SAMPLE

Each tablet contains:
Naproxen, USP ..... 500 mg

Store at controlled room temperature,
15°-30°C (59°-86°F).

N
3 0591-5818-02 4

DANBURY
PHARMACAL, INC.
DANBURY, CT 06810

NDC 0591-5818-02

NAPROXEN TABLETS, USP

500 mg

CAUTION: Federal law prohibits dispensing without prescription.

250 TABLETS

USUAL DOSAGE: See package insert for dosage and full prescribing information.

Dispense in a well-closed, light-resistant container as defined in the USP, with a child-resistant closure.

A-A

Control No. and Exp. Date

FEB 10 1995

APPROVED

LABEL
SAMPLE

Each tablet contains:
Naproxen, USP ..... 500 mg

Store at controlled room temperature,
15°-30°C (59°-86°F).

N 3 0591-5818-01 7

DANBURY
PHARMACAL, INC.
DANBURY, CT 06810

NDC 0591-5818-01

NAPROXEN TABLETS, USP

500 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 TABLETS

USUAL DOSAGE: See package insert for dosage and full prescribing information.

Dispense in a well-closed, light-resistant container as defined in the USP, with a child-resistant closure.

A-A

Control No. and Exp. Date

LABEL

SAMPLE

Each tablet contains:
Naproxen, USP ..... 500 mg

Store at controlled room temperature,
15°-30°C (59°-86°F).

N 3 0591-5818-01 7

DANBURY
PHARMACAL, INC.
DANBURY, CT 06810

NDC 0591-5818-01

NAPROXEN TABLETS, USP

500 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 TABLETS

USUAL DOSAGE: See package insert for dosage and full prescribing information.

Dispense in a well-closed, light-resistant container as defined in the USP, with a child-resistant closure.

A-A

Control No. and Exp. Date

LABEL

SAMPLE

0591-5818-00

Each tablet contains:
Naproxen, USP ..... 500 mg
Store at controlled room temperature, 15°-30°C (59°-86°F).

DANBURY
PHARMACAL, INC.

NDC 0591-5818-00
NAPROXEN
TABLETS, USP
500 mg
CAUTION: Federal law prohibits dispensing without prescription.
50 TABLETS

ORAL DOSAGE: See package insert for dosage and full prescribing information.
Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure.
Control No. and Exp. Date

LABEL
SAMPLE

0591-5818-00

Each tablet contains:
Naproxen, USP ..... 500 mg
Store at controlled room temperature, 15°-30°C (59°-86°F).

DANBURY
PHARMACAL, INC.

NDC 0591-5818-00
NAPROXEN
TABLETS, USP
500 mg
CAUTION: Federal law prohibits dispensing without prescription.
50 TABLETS

ORAL DOSAGE: See package insert for dosage and full prescribing information.
Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure.
Control No. and Exp. Date

LABEL
SAMPLE

0591-5818-30

Each tablet contains:
Naproxen, USP ..... 500 mg
Store at controlled room temperature, 15°-30°C (59°-86°F).

DANBURY
PHARMACAL INC

NDC 0591-5818-30
NAPROXEN
TABLETS, USP
500 mg
CAUTION: Federal law prohibits dispensing without prescription
30 TABLETS

USUAL DOSAGE: See package insert for dosage and full prescribing information.
Dispense in a well-closed, light-resistant container as defined in the USP, with a child-resistant closure.
A.
Control No. and Exp. Date

LABEL
SAMPLE

0591-5818-30

Each tablet contains:
Naproxen, USP ..... 500 mg
Store at controlled room temperature, 15°-30°C (59°-86°F).

DANBURY
PHARMACAL INC.

NDC 0591-5818-30
NAPROXEN
TABLETS, USP
500 mg
CAUTION: Federal law prohibits dispensing without prescription.
30 TABLETS

USUAL DOSAGE: See package insert for dosage and full prescribing information.
Dispense in a well-closed, light-resistant container as defined in the USP, with a child-resistant closure.
A.
Control No. and Exp. Date

LABEL
SAMPLE

DANBURY
PHARMACAL, INC.
DANBURY, CT 06810

NDC 0591-5817-04

NAPROXEN TABLETS, USP

375 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 TABLETS

Each tablet contains:
Naproxen, USP ..... 375 mg

Store at controlled room temperature,
15°-30°C (59°-86°F).

USUAL DOSAGE: See package insert for dosage and full prescribing information.

Dispense in a well-closed, light-resistant container as defined in the USP, with a child-resistant closure.

A-A [illegible] 10 [illegible]

Control No. and Exp. Date

LABEL
SAMPLE

DANBURY
PHARMACAL, INC.
DANBURY, CT 06810

NDC 0591-5817-04

NAPROXEN TABLETS, USP

375 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 TABLETS

Each tablet contains:
Naproxen, USP ..... 375 mg

Store at controlled room temperature,
15°-30°C (59°-86°F).

USUAL DOSAGE: See package insert for dosage and full prescribing information.

Dispense in a well-closed, light-resistant container as defined in the USP, with a child-resistant closure.

A-A 10

Control No. and Exp. Date

LABEL
SAMPLE

Each tablet contains:
Naproxen, USP ..... 375 mg

Store at controlled room temperature,
15°-30°C (59°-86°F).

N
3 0591-5817-03 4

DANBURY
PHARMACAL, INC.
DANBURY, CT 06810

NDC 0591-5817-03

NAPROXEN TABLETS, USP

375 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 TABLETS

USUAL DOSAGE: See package insert for dosage and full prescribing information.

Dispense in a well-closed, light-resistant container as defined in the USP, with a child-resistant closure.

A-A

Control No. and Exp. Date

LABEL
SAMPLE

Each tablet contains:
Naproxen, USP ..... 375 mg

Store at controlled room temperature,
15°-30°C (59°-86°F).

N
3 0591-5817-03 4

DANBURY
PHARMACAL, INC.
DANBURY, CT 06810

NDC 0591-5817-03

NAPROXEN TABLETS, USP

375 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 TABLETS

USUAL DOSAGE: See package insert for dosage and full prescribing information.

Dispense in a well-closed, light-resistant container as defined in the USP, with a child-resistant closure.

A-A

Control No. and Exp. Date

LABEL
SAMPLE

DANBURY
PHARMACAL, INC.
DANBURY CT 06810

NDC 0591-5817-02

NAPROXEN TABLETS, USP

375 mg

CAUTION: Federal law prohibits dispensing without prescription.

250 TABLETS

Each tablet contains:
Naproxen, USP ..... 375 mg

Store at controlled room temperature, 15°-30°C (59°-86°F).

N 3 0591-5817-02 7

USUAL DOSAGE: See package insert for dosage and for prescribing information.

Dispense in a well-closed, light-resistant container as defined in the USP, with a child-resistant closure.

A-A ____ Control No. and Exp. Date

APPROVED
FEB 10 1998
LABEL
SAMPLE

DANBURY
PHARMACAL, INC.

NDC 0591-5817-02

NAPROXEN TABLETS, USP

375 mg

CAUTION: Federal law prohibits dispensing without prescription.

250 TABLETS

Each tablet contains:
Naproxen, USP ..... 375 mg

Store at controlled room temperature, 15°-30°C (59°-86°F).

N 3 0591-5817-02 7

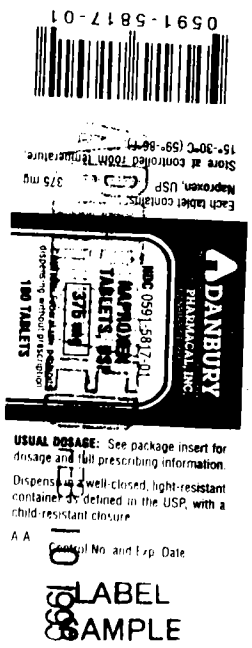
USUAL DOSAGE: See package insert for dosage and for prescribing information.

Dispense in a well-closed, light-resistant container as defined in the USP, with a child-resistant closure.

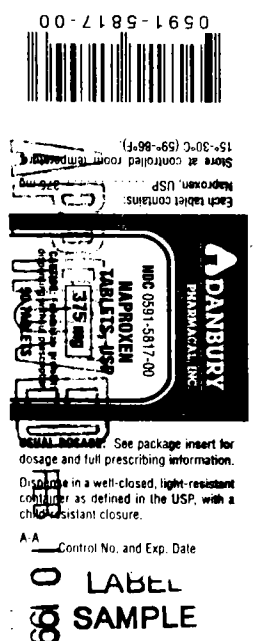
A-A ____ Control No. and Exp. Date

APPROVED
FEB 10 1998
LABEL
SAMPLE


0591-5817-01
DANBURY
PHARMACAL, INC.
NAPROXEN
TABLETS, USP
375 mg
100 TABLETS
USUAL DOSAGE: See package insert for dosage and full prescribing information.
Dispense in a well-closed, light-resistant container as defined in the USP, with a child-resistant closure.
A-A
Control No. and Exp. Date
LABEL
SAMPLE


0591-5817-01
DANBURY
PHARMACAL, INC.
NAPROXEN
TABLETS, USP
375 mg
100 TABLETS
USUAL DOSAGE: See package insert for dosage and full prescribing information.
Dispense in a well-closed, light-resistant container as defined in the USP, with a child-resistant closure.
A-A
Control No. and Exp. Date
LABEL
SAMPLE


0591-5817-00
Each tablet contains:
Naproxen, USP 375 mg
Store at controlled room temperature,
15°-30°C (59°-86°F).
DANBURY
PHARMACAL, INC.
NDC 0591-5817-00
NAPROXEN
TABLETS, USP
375 mg
100 TABLETS
USUAL DOSAGE: See package insert for dosage and full prescribing information.
Dispense in a well-closed, light-resistant container as defined in the USP, with a child-resistant closure.
A-A
Control No. and Exp. Date
LABEL
SAMPLE


0591-5817-00
Each tablet contains:
Naproxen, USP 375 mg
Store at controlled room temperature,
15°-30°C (59°-86°F).
DANBURY
PHARMACAL, INC.
NDC 0591-5817-00
NAPROXEN
TABLETS, USP
375 mg
100 TABLETS
USUAL DOSAGE: See package insert for dosage and full prescribing information.
Dispense in a well-closed, light-resistant container as defined in the USP, with a child-resistant closure.
A-A
Control No. and Exp. Date
LABEL
SAMPLE

0591-5817-30

Each tablet contains:
Naproxen, USP 375 mg

Store at controlled room temperature.
15°-30°C (59°-86°F).

DANBURY
PHARMACAL INC

NDC 0591-5817-30

NAPROXEN
TABLETS, USP
375 mg

Caution: Federal law prohibits
dispensing without prescription

30 TABLETS

PROOF

USUAL DOSAGE - See package insert for dosage and other prescribing information.

Dispensed in a well-closed, light-resistant container as defined in the USP, with a child-resistant closure.

A-A

Control No. and Exp. Date

1995

LABEL
SAMPLE

0591-5817-30

Each tablet contains:
Naproxen, USP 375 mg

Store at controlled room temperature.
15°-30°C (59°-86°F).

DANBURY
PHARMACAL INC.

NDC 0591-5817-30

NAPROXEN
TABLETS, USP
375 mg

Caution: Federal law prohibits
dispensing without prescription

30 TABLETS

PROOF

USUAL DOSAGE - See package insert for dosage and full prescribing information.

Dispensed in a well-closed, light-resistant container as defined in the USP, with a child-resistant closure.

A-A

Control No. and Exp. Date

1995

LABEL
SAMPLE

Each tablet contains:
Naproxen, USP ..... 250 mg

Store at controlled room temperature,
15°-30°C (59°-86°F).

N 3 0591-5816-04 4

DANBURY
PHARMACAL, INC.
DANBURY, CT 06810

NDC 0591-5816-04

NAPROXEN TABLETS, USP

250 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 TABLETS

USUAL DOSAGE: See package insert for dosage and full prescribing information.

Dispense in a well-closed, light-resistant container as defined in the USP, with a child-resistant closure.

A-A

Control No. and Exp. Date

LABEL
SAMPLE

FEB 10 1995

APPROVED

Each tablet contains:
Naproxen, USP ..... 250 mg

Store at controlled room temperature,
15°-30°C (59°-86°F).

N 3 0591-5816-04 4

DANBURY
PHARMACAL, INC.
DANBURY, CT 06810

NDC 0591-5816-04

NAPROXEN TABLETS, USP

250 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 TABLETS

USUAL DOSAGE: See package insert for dosage and full prescribing information.

Dispense in a well-closed, light-resistant container as defined in the USP, with a child-resistant closure.

A-A

Control No. and Exp. Date

LABEL
SAMPLE

FEB 10 1995

APPROVED

DANBURY
PHARMACAL, INC.
DANBURY, CT 06810

NDC 0591-5816-03

NAPROXEN TABLETS, USP

250 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 TABLETS

Each tablet contains:
Naproxen, USP ..... 250 mg

Store at controlled room temperature.
15°-30°C (59°-86°F).

USUAL DOSAGE: See package insert for dosage and full prescribing information.

Dispense in tight, light-resistant container as defined in the USP with a child-resistant closure.

A-A

Control No. and Exp. Date

FEB 10 95

APPROVED

LABEL SAMPLE

N 3 0591-5816-03 7

DANBURY
PHARMACAL, INC.
DANBURY, CT 06810

NDC 0591-5816-03

NAPROXEN TABLETS, USP

250 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 TABLETS

Each tablet contains:
Naproxen, USP ..... 250 mg

Store at controlled room temperature.
15°-30°C (59°-86°F).

USUAL DOSAGE: See package insert for dosage and full prescribing information.

Dispense in tight, light-resistant container as defined in the USP with a child-resistant closure.

A-A

Control No. and Exp. Date

FEB 10 95

APPROVED

LABEL SAMPLE

N 3 0591-5816-03 7

DANBURY
PHARMACAL, INC.

NDC 0591-5816-02

NAPROXEN TABLETS, USP

250 mg

CAUTION: Federal law prohibits dispensing without prescription.

250 TABLETS

USUAL DOSAGE: See package insert for dosage and full prescribing information.

Dispense in a well-closed, light-resistant container as defined in the USP, with a child-resistant closure.

A-AL

Control No. and Exp. Date

LABEL
SAMPLE

Each tablet contains:

Naproxen, USP ..... 250 mg

Store at controlled room temperature, 15°-30°C (59°-86°F).

N
3 0591-5816-02 0

DANBURY
PHARMACAL, INC.

NDC 0591-5816-02

NAPROXEN TABLETS, USP

250 mg

CAUTION: Federal law prohibits dispensing without prescription.

250 TABLETS

USUAL DOSAGE: See package insert for dosage and full prescribing information.

Dispense in a well-closed, light-resistant container as defined in the USP, with a child-resistant closure.

A-AL

Control No. and Exp. Date

LABEL
SAMPLE

Each tablet contains:

Naproxen, USP ..... 250 mg

Store at controlled room temperature, 15°-30°C (59°-86°F).

N
3 0591-5816-02 0

0591-5816-01
0 995
Each tablet contains:
Naproxen, USP ..... mg
Store at controlled room temperature,
15°-30°C (59°-86°F).
DANBURY
PHARMACAL, INC.
NDC 0591-5816-01
NAPROXEN
TABLETS, USP
250 mg
100 TABLETS
Dispense in a well-closed, light-resistant
container as defined in the USP, with a
A-A
and Exp. Date
LABEL
SAMPLE

0591-5816-01
Each tablet contains:
Naproxen, USP ..... mg
Store at controlled room temperature,
15°-30°C (59°-86°F).
DANBURY
PHARMACAL, INC.
NDC 0591-5816-01
NAPROXEN
TABLETS, USP
250 mg
100 TABLETS
Dispense in a well-closed, light-resistant
container as defined in the USP, with a
and Exp. Date
LABEL
SAMPLE

0591-5816-00
Each tablet contains:
Naproxen, USP ..... 250 mg
Store at controlled room temperature,
15°-30°C (59°-86°F).
DANBURY
PHARMACAL INC
NAPROXEN
TABLETS, USP
250 mg
50 TABLETS
APPROVED
LABEL
SAMPLE

0591-5816-00
Each tablet contains:
Naproxen, USP ..... 250 mg
Store at controlled room temperature,
15°-30°C (59°-86°F).
DANBURY
PHARMACAL INC
NDC 0591-5816-00
NAPROXEN
TABLETS, USP
250 mg
50 TABLETS
APPROVED
LABEL
SAMPLE

0591-5816-30
DANBURY
PHARMACAL INC
NAPROXEN
TABLETS USP
250 mg
CAUTION: Federal law prohibits dispensing without prescription.
30 TABLETS
LABEL
SAMPLE

0591-5816-30
DANBURY
PHARMACAL INC
NAPROXEN
TABLETS USP
250 mg
CAUTION: Federal law prohibits dispensing without prescription.
30 TABLETS
LABEL
SAMPLE

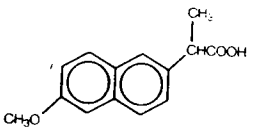
NAPROXEN TABLETS, USP

DESCRIPTION

Naproxen is a member of the arylacetic acid group of nonsteroidal anti-inflammatory drugs.

The chemical name for naproxen is 2-naphthaleneacetic acid, 6-methoxy-α-methyl-, (α).

The structural formula is represented below:



$C_{14}H_{14}O_3$ M.W. 230.26

Naproxen is a practically odorless, white to off-white crystalline substance. It is lipid soluble, practically insoluble in water at low pH and freely soluble in water at high pH.

Naproxen Tablets, USP for oral administration each contain 250 mg, 375 mg or 500 mg of naproxen.

In addition, Naproxen Tablets, USP 250 mg, 375 mg and 500 mg contain the following inactive ingredients: croscarmellose sodium, magnesium stearate and povidone.

Naproxen Tablets, USP 250 mg and 500 mg also contain: D&C Yellow No. 10 aluminum lake and FD&C Blue No. 2 aluminum lake.

Naproxen Tablets, USP 375 mg also contain: FD&C Red No. 40 aluminum lake and FD&C Blue No. 2 aluminum lake.

CLINICAL PHARMACOLOGY

Naproxen is a nonsteroidal anti-inflammatory drug with analgesic and antipyretic properties. Naproxen sodium, the sodium salt of naproxen, has been developed as an analgesic because it is more rapidly absorbed. The naproxen anion inhibits prostaglandin synthesis but beyond this its mode of action is unknown.

Naproxen is rapidly and completely absorbed from the gastrointestinal tract. After administration of naproxen, peak plasma levels of naproxen anion are attained in 2 to 4 hours, with steady-state conditions normally achieved after 4-5 doses. The mean biological half-life of the anion in humans is approximately 13 hours, and at therapeutic levels it is greater than 99% albumin bound. At doses of naproxen greater than 500 mg/day there is a lack of dose proportionality due to an increase in clearance caused by saturation of plasma proteins at higher doses. Approximately 95% of the dose is excreted in the urine, primarily as naproxen, 6-O-desmethyl naproxen or their conjugates. The rate of excretion has been found to coincide closely with the rate of drug disappearance from the plasma. The drug does not induce metabolizing enzymes.

In children of 5 to 16 years of age with arthritis, plasma naproxen levels following a 5 mg/kg single dose of suspension were found to be similar to those found in normal adults following a 500 mg dose. The terminal half-life appears to be similar in children and adults. Pharmacokinetic studies of naproxen were not performed in children of less than 5 years of age.

The drug was studied in patients with rheumatoid arthritis, osteoarthritis, juvenile arthritis, ankylosing spondylitis, tendonitis and bursitis, and acute gout. It is not a corticosteroid. Improvement in patients treated for rheumatoid arthritis has been demonstrated by a reduction in joint swelling, a reduction in pain, a reduction in duration of morning stiffness, a reduction in disease activity as assessed by both the investigator and patient, and by increased mobility as demonstrated by a reduction in walking time.

In patients with osteoarthritis, the therapeutic action of the drug has been shown by a reduction in joint pain or tenderness, an increase in range of motion in knee joints, increased mobility as demonstrated by a reduction in walking time, and improvement in capacity to perform activities of daily living impaired by the disease.

In clinical studies of patients with rheumatoid arthritis, osteoarthritis, and juvenile arthritis, the drug has been shown to be comparable to aspirin and indomethacin in controlling the aforementioned measures of disease activity, but the frequency and severity of the minor gastrointestinal adverse effects (nausea, dyspepsia, heartburn) and nervous system adverse effects (tinnitus, dizziness, lightheadedness) were less than in both the aspirin- and indomethacin-treated patients. It is not known whether the drug causes less peptic ulceration than aspirin.

In patients with ankylosing spondylitis, the drug has been shown to decrease night pain, morning stiffness and pain at rest. In double-blind studies the drug was shown to be as effective as aspirin, but with fewer side effects.

In patients with acute gout, a favorable response to the drug was shown by significant clearing of inflammatory changes (e.g., decrease in swelling, heat) within 24-48 hours, as well as by relief of pain and tenderness.

The drug may be used safely in combination with gold salts and/or corticosteroids; however, in controlled clinical trials, when added to the regimen of patients receiving corticosteroids it did not appear to produce greater improvement than seen with corticosteroids alone. Whether the drug could be used in conjunction with partially effective doses of corticosteroid for a "steroid-sparing" effect has not been adequately studied. When added to the regimen of patients receiving gold salts the drug did result in greater improvement. Its use in combination with salicylates is not recommended because data are inadequate to demonstrate that the drug produces greater improvement over [illegible]

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Generally, improvement due to the drug has not been found to be dependent on age, sex, severity or duration of disease.

In clinical trials in patients with osteoarthritis and rheumatoid arthritis comparing treatments of 750 mg per day with 1,500 mg per day, there were trends toward increased efficacy with the higher dose and a more marked increase in adverse reactions, particularly gastrointestinal reactions severe enough to cause the patient to leave the trial, which approximately doubled.

The drug was studied in patients with mild to moderate pain, and pain relief was obtained within 1 hour. It is not a narcotic and is not a CNS-acting drug. Controlled double-blind studies have demonstrated the analgesic properties of the drug in, for example, postoperative, post-partum, orthopedic and uterine contraction pain and dysmenorrhea. In dysmenorrheic patients, the drug reduces the level of prostaglandins in the uterus, which correlates with a reduction in the frequency and severity of uterine contractions. Analgesic action has been shown by such measures as a reduction of pain intensity scores, increase in pain relief scores, decrease in numbers of patients requiring additional analgesic medication, and delay in time for required remedication. The analgesic effect has been found to last for up to 7 hours.

In ^{51}Cr blood loss and gastroscopy studies with normal volunteers, daily administration of 1000 mg of the drug has been demonstrated to cause statistically significantly less gastric bleeding and erosion than 3250 mg of aspirin.

INDICATIONS AND USAGE

Naproxen tablets are indicated for the treatment of rheumatoid arthritis, osteoarthritis, juvenile arthritis, ankylosing spondylitis, tendinitis and bursitis, and acute gout. They are also indicated in the relief of mild to moderate pain and for the treatment of primary dysmenorrhea.

CONTRAINDICATIONS

The drug is contraindicated in patients who have had allergic reactions to naproxen or to naproxen sodium. It is also contraindicated in patients in whom aspirin or other nonsteroidal anti-inflammatory/analgesic drugs induce the syndrome of asthma, rhinitis, and nasal polyps. Both types of reactions have the potential of being fatal. Anaphylactoid reactions to naproxen or naproxen sodium, whether of the true allergic type or the pharmacologic idiosyncratic (e.g., aspirin syndrome) type, usually but not always occur in patients with a known history of such reactions. Therefore, careful questioning of patients for such things as asthma, nasal polyps, urticaria, and hypotension associated with nonsteroidal anti-inflammatory drugs before starting therapy is important. In addition, if such symptoms occur during therapy, treatment should be discontinued.

WARNINGS

Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy

Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease (such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PRECAUTIONS

General

NAPROXEN SHOULD NOT BE USED CONCOMITANTLY WITH THE RELATED DRUG NAPROXEN SODIUM SINCE THEY BOTH CIRCULATE IN PLASMA AS THE NAPROXEN ANION.

Renal Effects

As with other nonsteroidal anti-inflammatory drugs, long-term administration of naproxen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of nonsteroidal anti-inflammatory therapy is typically followed by recovery to the pretreatment state.

Naproxen and its metabolites are eliminated primarily by the kidneys, therefore, the drug should be used with great caution in patients with significantly impaired renal function and the monitoring of serum creatinine and/or creatinine clearance is advised in these patients. Caution should be used when the drug is given to patients with creatinine clearance of less than 20 mL/minute because accumulation of naproxen metabolites has been seen in such patients.

Chronic alcoholic liver disease and probably other forms of cirrhosis reduce the total plasma concentration of naproxen, but the plasma concentration of unbound naproxen is increased. Caution is advised when high doses are required and some adjustment of

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Chronic alcoholic liver disease and probably other forms of cirrhosis reduce the total plasma concentration of naproxen, but the plasma concentration of unbound naproxen is increased. Caution is advised when high doses are required and some adjustment of dosage may be required in these patients. It is prudent to use the lowest effective dose.

One study indicates that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly. Caution is advised when high doses are required and some adjustment of dosage may be required in elderly patients.

As with other drugs used in the elderly, it is prudent to use the lowest effective dose. As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. The SGPT (ALT) test is probably the most sensitive indicator of liver dysfunction. Moderate (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with this drug. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with this drug as with other nonsteroidal anti-inflammatory drugs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), this drug should be discontinued.

If steroid dosage is reduced or eliminated during therapy, the steroid dosage should be reduced slowly and the patients must be observed closely for any evidence of adverse effects, including adrenal insufficiency and exacerbation of symptoms of arthritis.

Patients with initial hemoglobin values of 10 grams or less who are to receive long-term therapy should have hemoglobin values determined periodically.

Peripheral edema has been observed in some patients. For this reason, the drug should be used with caution in patients with fluid retention, hypertension or heart failure.

The antipyretic and anti-inflammatory activities of the drug may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed non-infectious, non-inflammatory painful conditions.

Because of adverse eye findings in animal studies with drugs of this class, it is recommended that ophthalmic studies be carried out if any change or disturbance in vision occurs.

Information for Patients

Naproxen, like other drugs of its class, is not free of side effects. The side effects of these drugs can cause discomfort and, rarely, there are more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes.

NSAIDs (Nonsteroidal Anti-Inflammatory Drugs) are often essential agents in the management of arthritis and have a major role in the treatment of pain, but they also may be commonly employed for conditions which are less serious.

Physicians may wish to discuss with their patients the potential risks (see **WARNINGS, PRECAUTIONS,** and **ADVERSE REACTIONS** sections) and likely benefits of NSAID treatment, particularly when the drugs are used for less serious conditions where treatment without NSAIDs may represent an acceptable alternative to both the patient and physician.

Caution should be exercised by patients whose activities require alertness if they experience drowsiness, dizziness, vertigo or depression during therapy with the drug.

Laboratory Tests

Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding and should inform them of the importance of this follow-up (see **WARNINGS, Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy**).

Drug Interactions

In vitro studies have shown that naproxen anion, because of its affinity for protein, may displace from their binding sites other drugs which are also albumin-bound. Theoretically, the naproxen anion itself could likewise be displaced. Short-term controlled studies failed to show that taking the drug significantly affects prothrombin times when administered to individuals on coumarin-type anticoagulants. Caution is advised nonetheless, since interactions have been seen with other nonsteroidal agents of this class. Similarly, patients receiving the drug and a hydantoin, sulfonamide or sulfonylurea should be observed for signs of toxicity to these drugs.

The natriuretic effect of furosemide has been reported to be inhibited by some drugs of this class. Inhibition of renal lithium clearance leading to increases in plasma lithium concentrations has also been reported.

This and other nonsteroidal anti-inflammatory drugs can reduce the antihypertensive effect of propranolol and other beta-blockers.

Probenecid given concurrently increases naproxen anion plasma levels and extends its plasma half-life significantly.

Caution should be used if this drug is administered concomitantly with methotrexate. Naproxen and other nonsteroidal anti-inflammatory drugs have been reported to reduce the tubular secretion of methotrexate in an animal model, possibly enhancing the toxicity of that drug.

Drug/Laboratory Test Interactions

The drug may decrease platelet aggregation and prolong bleeding time. This effect should be kept in mind when bleeding times are determined.

The administration of the drug may result in increased urinary values for 17-ketogenic steroids because of an interaction between the drug and/or its metabolites with m-dinitrobenzene used in this assay. Although 17-hydroxy-corticosteroid measurements (Porter-Silber test) do not appear to be artifactually altered, it is suggested that therapy with the drug be temporarily discontinued 72 hours before adrenal function tests are performed.

The drug may interfere with some urinary assays of 5-hydroxy indoleacetic acid (5HIAA).

Carcinogenesis

A two-year study was performed in rats to evaluate the carcinogenic potential of the drug. No evidence of carcinogenicity was found.

Pregnancy

Teratogenic Effects

Pregnancy Category B

Reproduction studies have been performed in rats, rabbits and mice at doses up to six times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to the drug. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, the drug should not be used during pregnancy unless clearly needed. Because of the known effect of drugs of this class on the human fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided.

Non-teratogenic Effects

As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats.

Nursing Mothers

The naproxen anion has been found in the milk of lactating women at a concentration of approximately 1% of that found in the plasma. Because of the possible adverse effects of prostaglandin-inhibiting drugs on neonates, use in nursing mothers should be avoided.

Pediatric Use

Safety and effectiveness in children below the age of 2 years have not been established. Pediatric dosing recommendations for juvenile arthritis are based on well-controlled studies (see **DOSAGE AND ADMINISTRATION**). There are no adequate effectiveness or dose-response data for other pediatric conditions, but the experience in juvenile arthritis and other use experience have established that single doses of 2.5-5 mg/kg, with total daily dose not exceeding 15 mg/kg/day, are safe in children over 2 years of age.

ADVERSE REACTIONS

The following adverse reactions are divided into 3 parts based on frequency and likelihood of causal relationship to naproxen.

Incidence greater than 1%

Probable Causal Relationship

Adverse reactions reported in controlled clinical trials in 960 patients treated for rheumatoid arthritis or osteoarthritis are listed below. In general, these reactions were reported 2 to 10 times more frequently than they were in studies in the 962 patients treated for mild to moderate pain or for dysmenorrhea.

A clinical study found gastrointestinal reactions to be more frequent and more severe in rheumatoid arthritis patients taking 1,500 mg naproxen daily compared to those taking 750 mg daily (see **CLINICAL PHARMACOLOGY**).

In controlled clinical trials with about 80 children and in well-monitored open studies with about 400 children with juvenile arthritis, the incidences of rash and prolonged bleeding times were increased, the incidences of gastrointestinal and central nervous system reactions were about the same, and the incidences of other reactions were lower in children than in adults.

Gastrointestinal

The most frequent complaints reported related to the gastrointestinal tract. They were: constipation*, heartburn*, abdominal pain*, nausea*, dyspepsia, diarrhea, stomatitis.

Central Nervous System

vertigo.

Dermatologic

itching (pruritus)*, skin eruptions*, ecchymoses*, sweating, purpura.

Special Senses

Tinnitus*, hearing disturbances, visual disturbances

those taking 750 mg daily (see CLINICAL PHARMACOLOGY).

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Gastrointestinal

The most frequent complaints reported related to the gastrointestinal tract. They were: constipation*, heartburn*, abdominal pain*, nausea*, dyspepsia, diarrhea, stomatitis.

Central Nervous System

Headache*, dizziness*, drowsiness*, lightheadedness, vertigo.

Dermatologic

Itching (pruritus)*, skin eruptions*, ecchymoses*, sweating, purpura.

Special Senses

Tinnitus*, hearing disturbances, visual disturbances.

Cardiovascular

Edema*, dyspnea*, palpitations.

General

Thirst.

*Incidence of reported reactions between 3% and 9%. These reactions occurring in less than 3% of the patients are unmarked.

Incidence less than 1%

Probable Causal Relationship

The following adverse reactions were reported less frequently than 1% during controlled clinical trials and through voluntary reports since marketing. The probability of a causal relationship exists between the drug and these adverse reactions.

Gastrointestinal

Abnormal liver function tests, colitis, gastrointestinal bleeding and/or perforation, hematemesis, jaundice, melena, peptic ulceration with bleeding and/or perforation, vomiting.

Renal

Glomerular nephritis, hematuria, interstitial nephritis, nephrotic syndrome, renal disease.

Hematologic

Agranulocytosis, eosinophilia, granulocytopenia, leukopenia, thrombocytopenia.

Central Nervous System

Depression, dream abnormalities, inability to concentrate, insomnia, malaise, myalgia and muscle weakness.

Dermatologic

Alopecia, photosensitive dermatitis, skin rashes.

Special Senses

Hearing impairment.

Cardiovascular

Congestive heart failure.

Respiratory

Eosinophilic pneumonitis.

General

Anaphylactoid reactions, menstrual disorders, pyrexia (chills and fever).

Causal Relationship Unknown

Other reactions have been reported in circumstances in which a causal relationship could not be established. However, in these rarely reported events, the possibility cannot be excluded. Therefore, these observations are being listed to serve as alerting information to the physicians:

Hematologic

Aplastic anemia, hemolytic anemia.

Central Nervous System

Cognitive dysfunction.

Dermatologic

Epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome, urticaria.

Gastrointestinal

Non-peptic gastrointestinal ulceration, ulcerative stomatitis.

Cardiovascular

Vasculitis

General

Angioneurotic edema, hyperglycemia, hypoglycemia

OVERDOSAGE

Significant overdosage may be characterized by drowsiness, heartburn, indigestion, nausea or vomiting. No evidence of toxicity or late sequelae have been reported 5 to 15 months after ingestion for 3 to 7 days of doses up to 3,000 mg of naproxen. One patient ingested a single dose of 25 g of naproxen and experienced mild nausea and indigestion. It is not known what dose of the drug would be life threatening. The oral LD_{50} of the drug is 543 mg/kg in rats, 1234 mg/kg in mice, 4110 mg/kg in hamsters and greater than 1000 mg/kg in dogs.

Should a patient ingest a large number of tablets, accidentally or purposefully, the stomach may be emptied and usual supportive measures employed. In animals 0.5 g/kg of activated charcoal was effective in reducing plasma levels of naproxen. Hemodialysis does not decrease the plasma concentration of naproxen because of the high degree of its protein binding.

DOSAGE AND ADMINISTRATION

For Rheumatoid Arthritis, Osteoarthritis, and Ankylosing Spondylitis

The recommended dose of naproxen in adults is 250 mg, 375 mg, or 500 mg twice daily (morning and evening). During long-term administration, the dose may be adjusted up or down depending on the clinical response of the patient. A lower daily dose may suffice for long-term administration. The morning and evening doses do not have to be equal in size and the administration of the drug more frequently than twice daily is not necessary. In patients who tolerate lower doses well, the dose may be increased to 1,500 mg per day for limited periods when a higher level of anti-inflammatory/analgesic activity is required. When treating such patients with the 1,500 mg/day dose, the physician should observe sufficient increased clinical benefits to offset the potential increased risk (see CLINICAL PHARMACOLOGY).

Symptomatic improvement in arthritis usually begins within 2 weeks. However, if improvement is not seen within this period, a trial for an additional 2 weeks should be considered.

For Juvenile Arthritis

The recommended total daily dose of naproxen is approximately 10 mg/kg given in 2 divided doses. When necessary, an oral suspension should be used for ease and flexibility in administering these doses.

For Acute Gout

The recommended starting dose of naproxen is 750 mg, followed by 250 mg every 8 hours until the attack has subsided.

For Mild to Moderate Pain, Primary Dysmenorrhea and Acute Tendinitis and Bursitis

The recommended starting dose of naproxen is 500 mg,

6

Usual Dosage

The recommended dose of naproxen in adults is 250 mg, 375 mg, or 500 mg twice daily (morning and evening). During long-term administration, the dose may be adjusted up or down depending on the clinical response of the patient. A lower daily dose may suffice for long-term administration. The morning and evening doses do not have to be equal in size and the administration of the drug more frequently than twice daily is not necessary. In patients who tolerate lower doses well, the dose may be increased to 1,500 mg per day for limited periods when a higher level of anti-inflammatory/analgesic activity is required. When treating such patients with the 1,500 mg/day dose, the physician should observe sufficient increased clinical benefits to offset the potential increased risk (see CLINICAL PHARMACOLOGY).

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For Acute Gout

The recommended starting dose of naproxen is 750 mg, followed by 250 mg every 8 hours until the attack has subsided.

For Mild to Moderate Pain, Primary Dysmenorrhea and Acute Tendinitis and Bursitis

The recommended starting dose of naproxen is 500 mg, followed by 250 mg every 6 to 8 hours as required. The total daily dose should not exceed 1,250 mg.

HOW SUPPLIED

Naproxen Tablets, USP 250 mg are unscored, round, light green tablets supplied in bottles of 30, 50, 100, 250, 500 and 1000.

Naproxen Tablets, USP 375 mg are unscored, capsule shape, lavender tablets supplied in bottles of 30, 50, 100, 250, 500 and 1000.

Naproxen Tablets, USP 500 mg are unscored, capsule shape, light green tablets supplied in bottles of 30, 50, 100, 250, 500 and 1000.

Dispense in a well-closed, light-resistant container with a child-resistant closure.

Store at controlled room temperature 15°-30°C (59°-86°F).

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by:
BARRETT PHARMACAL, INC.
Danbury, CT 06810

Revised: December 1993
5816,5817,5818

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074163

CHEMISTRY REVIEW(S)

DIV

1. CHEMIST'S REVIEW NO. 4

2. ANDA # 74-163

3. NAME AND ADDRESS OF APPLICANT
Danbury Pharmacal Inc.
Attention: Edward M. Cohen
131 West Street
Danbury, Connecticut 06810

7. NONPROPRIETARY NAME: Naproxen

9. AMENDMENTS AND OTHER DATES

December 31, 1991:	Original submission
March 13, 1992:	Submission of bio data (amendment)
April 12, 1993:	Bio data on product manufactured with Syntex DS
July 27, 1993:	Amendment in response to our NA letter dated June 1, 1993
August 26, 1993:	Correspondence containing chemistry and bio data
December 20, 1993:	Telephone amending updating the dissolution specs to the revised USP specs.

This review covers July 27, and December 20, 1993 amendments and review of chemistry portion of amendment dated August 26, 1993.

10. PHARMACOLOGICAL CATEGORY
Anti-inflammatory, analgesic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s): See checklist.

17. COMMENTS: Firm has submitted an adequate response to the remaining CMC issues.

18. CONCLUSIONS AND RECOMMENDATIONS: Approvable subject to satisfactory EER.

19. REVIEWER
D. Gill

DATE COMPLETED

cc: ANDA 74-163
Division File
DUP File
Field Copy

Endorsements:
HFD-623/D.Gill/1-7-94
HFD-623/J.Fan/ABC/1-13-94
X:\WPFILE\BRANCH1\GILL\N74163R4.DG
F/T by dvw/2-1-94

APPROVAL PACKAGE SUMMARY

ANDA # 74-163

FIRM: Danbury Pharmacal, Inc. **DRUG:** Naproxen

DOSAGE: Tablets **STRENGTH(s):** 250 mg, 375 mg, 500 mg

cGMP STATEMENT/EIR UPDATE STATUS:

cGMP: Satisfactory (page 24780)
EER update: Filed 12/10/93. Awaiting report.

BIO STUDY(ies)/BIOEQUIVALENCE STATUS:

Satisfactory per bio reviews dated April 14, 1992 and December 9, 1993.

METHODS VALIDATION (Including dosage form description):

USP drugs. FDA methods validation is not required.

STABILITY (Conditions, Containers, methods):
Bio batch?

Conditions: Schedule conforms to CDER Stability Guide. Testing parameters include assay, dissolution, impurities/degradants , , and physical appearance.

Containers: Smallest and largest; and are the same as described in the container section.

Method: Shown to be stability indicating.

Bio Batch: Stability batches are the same as used for bioequivalence studies or comparative dissolution studies.

LABELING REVIEW STATUS:

Satisfactory per worksheet dated 11.17.92.

STERILIZATION VALIDATION (If Applicable): N/A

BATCH SIZES:

BIO BATCHES (identity #, DS source):

Batch #: 04867C (500 mg)
Batch size: tablets
DS source:

Batch #: 05587C (500 mg)
Batch size: tablets
DS source:

Firm's NDS sources are OK -

are satisfactory per reviews dated 11/9/92 and 8/25/93, respectively.

Other Batches:

Strength	Batch #	Batch size (tablets)	DS source
250 mg	05066C		
375 mg	05067C		
250 mg	09996C		
375 mg	09997C		

STABILITY BATCHES (different from BIO BATCH, manuf. site, process)

Stability batches manufactured by at the facility, are the same as the bio batches.

PROPOSED PRODUCTION BATCH (same manuf. process, #s, quant.)

Manufacturing process is the same as for the test batch.

	Maximum production size	
250 mg	375 mg	500 mg

COMMENTS: Approvable subject to satisfactory EER.

cc: ANDA 74-163
Division File
Field Copy

Endorsements:

HFD-623/D.Gill/1-7-94
HFD-623/J.Fan/ABC/1-11-94
X:\WPFILE\BRANCH1\GILL\A74163.DG
F/T by dvw/1-31-94

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074163

BIOEQUIVALENCE REVIEWS

DEC - 9 1993

Naproxen Tablets
250 mg, 375 mg, and 500 mg
ANDA #74-163
Reviewer: YC Huang
74163SW.493

Danbury Pharmacal, Inc.
Danbury, CT
Submission date:
April 12, 1993
July 27, 1993
August 26, 1993

Review of A Bioequivalence Study
(Alternate supplier of drug substance)

Introduction The firm previously (12/31/91) submitted two *in vivo* bioequivalence studies comparing Danbury Naproxen Tablets, 500 mg (lot #04867C) to Syntex Naprosyn® (naproxen) Tablets, 500 mg (lot #61659) under fasting and nonfasting conditions. The test products of these studies were manufactured using naproxen raw material. Both studies had been found acceptable. The waivers of *in vivo* bioequivalence study requirements for the 250 mg and 375 mg strengths of the test products had also been granted.

The current submission contains the results of a bioequivalence study to support the use of as an alternate manufacturer of the bulk drug substance. The waiver requests for the 250 mg and 375 mg strengths of the test product have also been made. The submission of July 27, 1993, in response to the comments from Division of Chemistry, contains the dissolution data of 250 mg, 375 mg, and 500 mg tablets at both extremes of hardness ranges. The submission of August 26, 1993 contains the comparative dissolution data: test products 250 mg and 375 mg manufactured with bulk versus Syntex Naprosyn® 250 mg and 375 mg tablets.

Objective (1) To report the results of a bioequivalence study comparing Danbury Naproxen Tablets, 500 mg with Syntex Naprosyn® Tablets, 500 mg, and (2) To make a waiver request of in vivo study requirements for the firm's 250 mg and 375 mg naproxen tablets.

Products tested

Test
Naproxen Tablets, 500 mg (Danbury Pharmacal)
Lot No. 05587C
Assay: 99.6%
Content Uniformity: 100.7% - 105.8% (CV, 1.7%)
(Tests were performed at Danbury using procedure.)
Batch size: not reported

Reference
Naprosyn (naproxen) Tablets, 500 mg (Syntex Puerto Rico, Inc.)
Lot No. 43283
Assay: 100.3%
Content Uniformity: 86.8%-101.3% (CV, 5.15%)

(Tests were performed at
using
Batch size: not reported

Dosage 500 mg

Study design Randomized, two-way crossover study with a washout period of one week between drug administration

Protocol No. 10457

Subjects Twenty male subjects were enrolled in the study after being screened from the general population. The criteria for eligibility of subjects, including medical histories, physical examinations and laboratory tests, are listed in Clinical appendix I (page 7-4). The demographics of the subjects are as follows: age ranging from 20 to 46 years, height ranging from 64 to 77 inches, and weight ranging from 127 to 228 lbs.

Study site

Clinical study dates Phase I: January 21-25, 1993
Phase II: January 28-February 1, 1993

The phase I confinement period started on January 21, 1993 and ended on January 23, 1993. Drug was administered on January 22, 1993. The subjects were instructed to return to the facility on January 23-25 for the 36, 48, and 72 hour blood sample collections.

The phase II confinement period started on January 28, 1993 and ended on January 31, 1993. Drug was administered on January 29, 1993. The subjects were instructed to return to the facility on January 30 - February 1 for the 36, 48, and 72 hour sample collections.

Foods and fluids The subjects fasted for at least 10 hours prior to dosing and until 5 hours postdose. Water was allowed freely except within one hour of drug administration. Only the food served was allowed until 24 hours after drug administration. The menu was the same for both phases.

Drug administration Beginning at 8:00 a.m. (after an overnight fast) on each dosing day, the drug products (one 500 mg tablet) were administered with 240 mL of water according to the randomized

dosing schedule. All subjects remained ambulatory or seated until 4 hours postdose.

Subject monitoring Blood pressure and pulse were measured predose and at 4 and 24 hours postdose, after the subjects had been seated for 3 minutes. Temperature and respirations were also measured predose and 24 hours postdose. Smoking was not permitted from 1 hour prior to dosing until 4 hours post-dosing.

Blood sample collection Ten (10) milliliters of venous blood were obtained in Vacutainers with no anticoagulant at: 0 (predose), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 36, 48, and 72 hours.

Assay

Data analysis Individual and mean serum levels of naproxen were reported. The following pharmacokinetic parameters were calculated: AUC (0-t) and AUC (0-∞), where t is the last non-zero time point, Cmax, Tmax, elimination rate constant, and half-life. The geometric means were also calculated for AUC(0-t), AUC(0-∞), and Cmax.

Results The firm enrolled 20 subjects and 17 of them completed the study. Subjects #4, #8, and #19 did not complete phase II of the study. Subject #4 was withdrawn prior to phase II dosing because of a positive urine drug screen. Subjects #8 and #19 did not return for the 36-72 hour blood samples and/or phase II of the study.

The serum levels of naproxen were monitored for 72 hours after drug administration. Only 7 subjects had detectable serum concentrations at 72 hours. Table I summarizes the mean serum concentration of naproxen at each time point after each product. There was no significant difference ($p>0.05$) in the mean concentrations between the test and the reference products at any time point after dosing. There were also no statistically significant differences between the test and the reference products in the derived pharmacokinetic parameters (Table I). The serum concentration - time profile is shown in Figure 1. The ratios of AUC(0-t)/AUC(0-∞) after the test product ranged from (mean=0.906), except for subject #16 who had a lower ratio of 0.77. The ratios of AUC(0-t)/AUC(0-∞) after the reference product ranged from (mean 0.905), except for subject #16 who had a ratio of 0.79. Table II shows the results of the calculation of 90% confidence intervals. The 90% confidence intervals for AUC(0-t), AUC(0-∞), and Cmax were within the range of 80-120% for the non-transformed data and the test/reference ratios were 1.00, 1.00, and 1.02, respectively. The 90% confidence intervals for log-transformed AUC(0-t), AUC(0-∞), and Cmax were within the range of 80-125% and the test/reference ratios, based on the geometric means, were 1.00, 1.00, and 1.02,

respectively.

The values of the pharmacokinetic parameters obtained from the present study are comparable to the results reported in the previous submission (12/31/91) for both test and reference products.

Adverse events One subject (#15) reported experiencing adverse events during the study. Both the elevated temperature and contact dermatitis experienced by the subject began prior to phase II dosing and were viewed as unrelated to the drug products, based on an examination by the physician.

Dissolution data Dissolution testing was conducted using the following conditions:

USP XXII Apparatus II (paddle) at 50 rpm (45-60 min: 200 rpm)
900 mL of 0.1M, pH 7.4 phosphate buffer
Sampling times: 5, 10, 15, 20, 30, 45, 60 minutes
Tolerance: NLT of naproxen dissolved in 45 minutes

Comments

1. In previous submissions (12/31/91 and 3/13/92), the firm had made a waiver request for the 500 mg tablet manufactured with naproxen as an alternate source of the active ingredient. The waiver request had been granted. In the current submission, the firm submitted the results of a bioequivalence study. The dissolution data supporting the previous waiver request and the current bioequivalence study all used the same lot of 500 mg naproxen tablets ,#05587C as the test product.

2. The serum naproxen concentration-time profiles for the test and reference products are comparable. The mean serum naproxen concentrations observed and the derived pharmacokinetic parameters were not statistically significantly different between the test and reference products.

3. The 90% confidence intervals for AUC(0-t), AUC(0-∞), and Cmax were within the range of 80-120% for the non-transformed data and the test/reference ratios were 1.00, 1.00, and 1.02, respectively. The 90% confidence intervals for log-transformed AUC(0-t), AUC(0-∞), and Cmax were within the range of 80-125% and the test/reference ratios, based on the geometric means, were 1.00, 1.00, and 1.02, respectively.

4. The assay validation data including the specificity,

sensitivity, linearity, accuracy, precision, recovery are acceptable. The reported sample stability, derived from freeze-thaw cycles and at room temperature for up to 48 hours, are acceptable.

5. The firm did not report the batch size of the test product used in the bioequivalence study.

6. The comparative dissolution data (test products manufactured with bulk versus Syntex Naprosyn® tablets) are acceptable.

7. The hardness of the test tablets seems to affect the initial dissolution rate at 5-minute time point. At the later times (10 - 60 minutes), the dissolution rates were comparable between the tablets with high or low hardness as reported. The results met the specifications of NLT of naproxen dissolved in 45 minutes.

8. The formulations for the test products (250 mg, 375 mg, and 500 mg strengths) are identical to those reported previously (12/31/91): The formulations of 250 mg and 375 mg tablets are proportionally similar to that of 500 mg tablets.

Recommendations

1. The request for a waiver of in vivo bioequivalence study requirements had been granted previously to the test product, Danbury Naproxen 500 mg Tablets manufactured with naproxen. The results of the bioequivalence study reported in the current submission (Danbury Naproxen 500 mg Tablets, lot #05587C vs Syntex Naprosyn® 500 mg Tablets, lot #43283) further support the bioequivalence between the test and reference products. Since the waiver request for using naproxen as an alternate source of the active ingredient had been granted previously, no further action is needed for the 500 mg strength.

2. The dissolution testing conducted by Danbury Pharmacal on its naproxen 250 mg tablets (lot # 09996C) and 375 mg tablets (lot #09997C), manufactured using naproxen bulk, is acceptable. The firm has conducted an acceptable in vivo bioequivalence study (current submission) comparing the test product (Danbury naproxen tablets, 500 mg, manufactured with naproxen bulk) with Syntex Naprosyn (naproxen) 500 mg tablets. In addition, the firm had previously conducted an acceptable in vivo bioequivalence study (submission dated 12/31/91), comparing the test product (Danbury naproxen tablets, 500 mg, manufactured with naproxen bulk) with Syntex Naprosyn (naproxen) 500 mg tablets. The

formulations for the 250 mg and 375 mg strengths are proportionally similar to the 500 mg strength of the test product which underwent bioequivalence testing. The waiver of in vivo bioequivalence study requirements for the 250 mg and 375 mg tablets of the test product is granted.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 0.1 M pH 7.4 phosphate buffer at 37 Celsius using USP XXII apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than of the labeled amount of the drug in the dosage form is dissolved in 45 minutes

The firm should be informed of the recommendations.

Yih-Chain Huang, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMhatre
FT INITIALED RMhatre

CONCUR

Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

Date 12/9/93

cc: ANDA #74-163 (original, duplicate), HFD-600 (Hare), HFD-630, HFC-130 (JAllen), HFD-344 (CViswanathan), HFD-658 (Mhatre, Huang), Drug File, Division File.

YCHuang/9-20-93,11-3-93/74163SW.493

Table I

Mean Serum Naproxen Concentrations (μg/mL) and The Derived Pharmacokinetic Parameters Following An Oral Dose of 500 mg Naproxen Tablet Under Fasting Conditions (N=17)

Time (hours)	Danbury Test Product	Syntex Reference Product
0	0	0
0.5	31.2 (24.8)	32.8 (24.9)
1.0	51.6 (29.3)	55.2 (24.9)
1.5	55.1 (24.8)	61.2 (19.0)
2.0	60.4 (17.7)	60.8 (16.6)
2.5	63.4 (13.5)	62.9 (14.1)
3.0	64.5 (12.6)	63.2 (12.6)
3.5	58.6 (10.4)	58.0 (10.3)
4.0	56.6 (7.90)	55.9 (8.72)
6.0	45.8 (7.05)	46.1 (7.45)
8.0	37.3 (8.03)	36.6 (7.44)
12.0	29.6 (7.06)	28.5 (6.08)
24.0	16.6 (5.76)	16.9 (6.50)
36.0	10.6 (5.12)	10.9 (5.20)
48.0	6.66(4.12)	6.94(4.35)
72.0	2.03(3.54)	1.96(3.34)
AUC(0-t),hr-μg/mL	1142 (345)	1145 (353)
AUC(0-∞)	1277 (480)	1279 (472)
Cmax,μg/mL	76.5 (14.3)	74.7 (11.2)
Tmax,hr	1.91 (1.03)	2.00 (0.95)
Kel (hr-1)	0.0429 (0.00972)	0.0419 (0.00906)
half-life (hr)	17.2 (5.22)	17.5 (4.77)
Ln AUC(0-t)	7.008 (0.252)	7.010 (0.250)
Geometric mean (CV)	1105 (25.6%)	1108 (25.4%)
Ln AUC(0-∞)	7.107 (0.285)	7.111 (0.278)
Geometric mean (CV)	1220 (29.1%)	1225 (28.3%)
Ln Cmax	4.320 (0.198)	4.302 (0.166)
Geometric mean (CV)	75.2 (20%)	73.8 (16.7%)

Values in the parenthesis are standard deviations, except where noted for geometric means. N=16 for 48-hour time point

Table II

Least Squares Means and 90% Confidence Intervals

Parameter	Test	Reference	T/R Ratio	90% C.I.
AUC(0-t)	1137	1139	1.00	0.98-1.02
AUC(0-∞)	1269	1271	1.00	0.98-1.01
Cmax	76.4	74.7	1.02	0.98-1.07
Tmax	1.90	1.98	0.96	
Ln AUC(0-t) Geometric mean	7.004 1101	7.006 1103	1.00	0.98-1.02
Ln AUC(0-∞) Geometric mean	7.102 1214	7.106 1219	1.00	0.98-1.01
Ln Cmax Geometric mean	4.318 75.0	4.301 73.8	1.02	0.97-1.07

Table III. In Vitro Dissolution Testing

Drug (Generic Name): Naproxen
Dose Strength: 500 mg, 375 mg, and 250 mg
ANDA No.: 74-163
Firm: Danbury Pharmacal
Submission Date: April 12, 1993
File Name: 74163SW.493

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle: X RPM: 50 (45-60 min. 200rpm)
No. Units Tested: 12
Medium: 0.1 M pH 7.4 Phosphate buffer Volume: 900 mL
Specifications: NLT in 45 minutes
Reference Drug: Syntex Naprosyn Tablets
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product (N=12) Lot # 05587C Strength(mg) 500 mg			Reference Product (N=12) Lot # 43283 Strength(mg) 500 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
5	84.0		7.4	96.2		4.1
10	95.6		4.9	100.7		1.6
15	99.2		3.4	101.6		1.0
20	100.3		2.7	101.7		0.8
30	101.1		2.2	101.8		0.9
45	101.3		2.2	102.0		0.8
60	101.3		2.2	101.9		1.0

Sampling Times (Minutes)	Test Product (N=6) Lot # 05066C Strength(mg) 250 mg Hardness:			Test Product (n=6) Lot # 05066C Strength(mg) 250 mg Hardness:		
	Mean %	Range	%CV	Mean %	Range	%CV
5	88.2		8.2	45.3		32.4
10	96.7		2.9	83.1		8.4

Sampling Times (Minutes)	Test Product (N=12) Lot # 09996C Strength(mg) 250 mg			Reference Product (N=12) Lot # 82986 Strength(mg) 250 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
5	70.4		10.5	91.6		7.5
10	91.0		6.5	99.9		2.0
15	97.8		3.5	101.0		0.7
20	100.0		2.0	101.4		1.1
30	101.3		1.2	101.5		1.2
45	101.4		1.4	101.5		1.2
60	101.5		1.5	101.5		1.2

Sampling Times (Minutes)	Test Product (N=12) Lot # 09997C Strength(mg) 375 mg			Reference Product (N=12) Lot # 93255 Strength(mg) 375 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
5	78.6		10.0	92.1		6.8
10	95.3		6.0	98.0		3.3
15	98.4		3.6	99.4		2.2
20	99.5		2.7	100.1		1.8
30	100.5		1.3	100.7		1.3
45	100.9		1.0	101.0		1.0
60	100.9		1.0	101.0		1.0

15	98.9			1.2	95.6		4.7
20	99.3			1.0	99.7		1.7
30	99.7			1.2	101.0		0.9
45	99.7			1.0	101.2		1.1
60	99.5			1.0	101.2		1.1

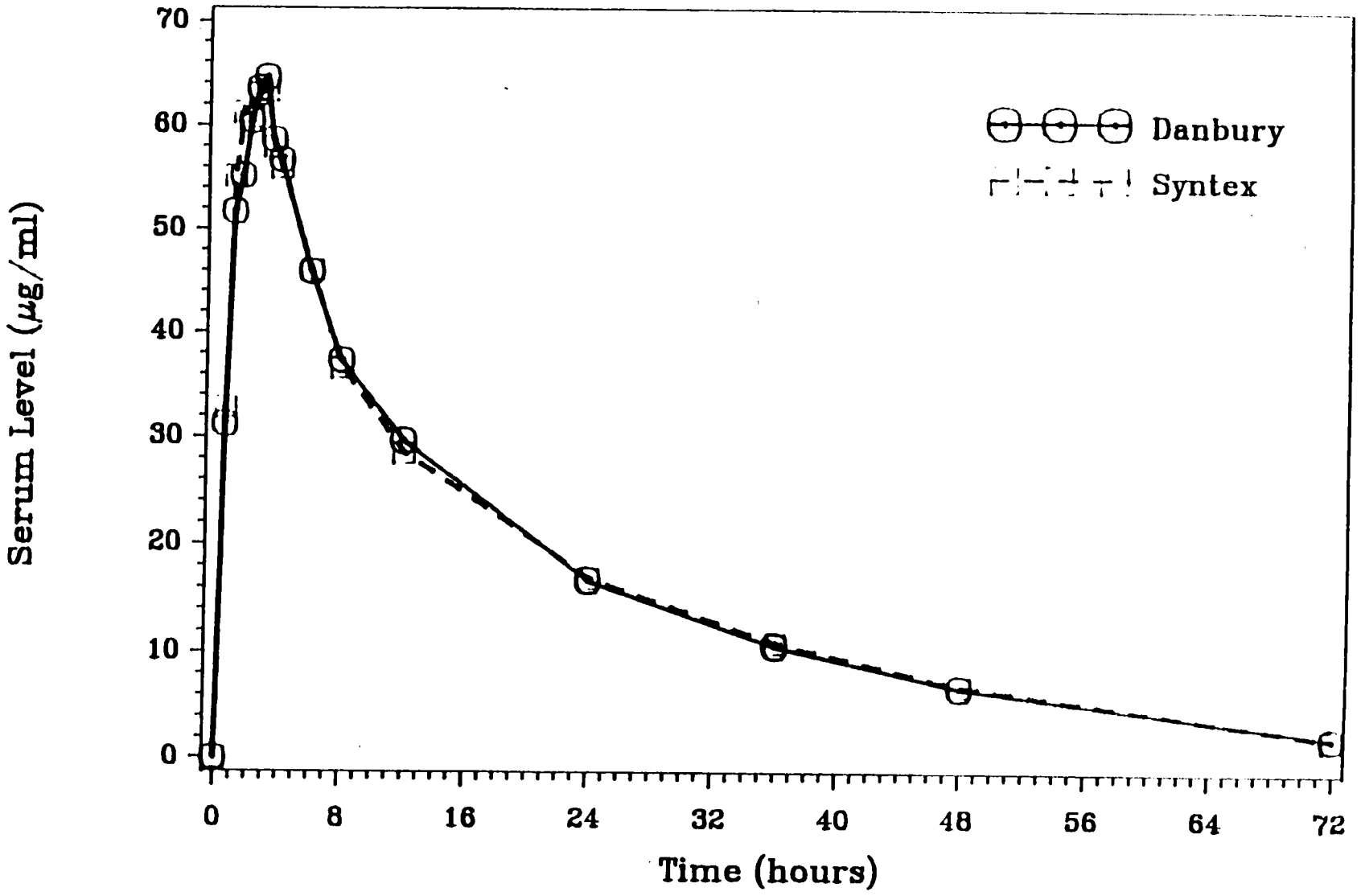
Sampling Times (Minutes)	Test Product (N=6) Lot # 05067C Strength(mg) 375 mg			Test Product (N=6) Lot # 05067C Strength(mg) 375 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
5	86.9		6.5	40.1		14.0
10	97.4		3.9	74.5		8.3
15	100.0		2.5	92.8		2.8
20	101.0		1.9	99.1		1.8
30	101.6		1.8	102.4		1.4
45	101.7		1.7	103.0		1.4
60	101.9		1.8	103.1		1.5

Sampling Times (Minutes)	Test Product (N=6) Lot # 05587C Strength(mg) 500 mg			Test Product (N=6) Lot # 05587C Strength(mg) 500 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
5	84.6		4.2	55.5		17.8
10	95.1		1.6	86.2		5.8
15	98.9		1.0	94.9		2.5
20	100.7		1.5	98.1		1.0
30	101.7		1.9	99.8		1.2
45	101.9		2.0	100.0		1.3
60	101.9		1.9	99.9		1.5

Fig. 1

Mean Naproxen Serum Levels

n = 17



APR 14 1992

Naproxen Tablets, USP
250 mg, 375 mg and 500 mg Tablets
ANDA #74-163
Reviewer: Moo Park
File Name: 74163SDW.D91

Danbury Pharmacal
Danbury, CT
Submission Date:
December 31, 1991
March 13, 1992

Review of Two Bioequivalence Studies, Dissolution Data and Waiver Requests

I. Objectives

To review:

- Danbury's in vivo bioequivalence studies under fasting and nonfasting conditions comparing its 500 mg strength Naproxen Tablets to the 500 mg strength Naprosyn^R Tablets of Syntex.
- Dissolution data for 250 mg, 375 mg and 500 mg strength test and reference products.
- Waiver requests for the 250 mg and 375 mg strength tablets.
- Waiver request for the 500 mg strength manufactured with naproxen as an alternate source of the active ingredient.

Danbury manufactured the 250 mg and 375 mg strength tablets with naproxen raw material. The 500 mg strength tablets were manufactured using naproxen from two different sources,

Danbury in cooperation with conducted the bioequivalence studies in a randomized 3-treatment, 3-period, cross over design to compare Danbury vs. Syntex and vs. Danbury. Danbury's test product (biobatch) was manufactured with naproxen raw material. 's test product was manufactured with naproxen raw material.

The bioequivalence study portion of Danbury's ANDA #74-163 is practically identical to that of (submission date: since the two firms are sharing the data of the same bioequivalence studies under fasting and nonfasting conditions.

II. Background

Naproxen is (S)-(+)-6-methoxy-α-methyl-2-naphthaleneacetic acid and exists as a single dextrorotatory isomer in pharmaceutical preparations. It has a carboxylic acid moiety with pKa 4.5, which exists mainly in the ionized form in plasma. The unionized form is lipid soluble. Naproxen is an orally administered nonsteroidal antiinflammatory drug (NSAID), which also has analgesic and

antipyretic properties. Currently approved indications for naproxen are: 1) treatment of rheumatoid arthritis, osteoarthritis, juvenile arthritis, ankylosing spondylitis, tendinitis, bursitis and acute gout; 2) relief of mild to moderate pain; and 3) treatment of primary dysmenorrhea.

At plasma pH, naproxen exists predominantly as the naproxen ion which reversibly binds the enzyme cyclooxygenase and inhibits prostaglandin synthesis, affecting conditions where overproduction of prostaglandins occurs. Other mechanisms of action may be possible.

Naproxen is rapidly and completely absorbed following oral administration with T_{max} values of 2 - 4 hr. After single oral doses of 100, 200, 300 and 500 mg, reported C_{max} values were 12, 25, 42 and 55 mcg/mL, respectively. Food may delay absorption by decreasing the rate of gastric emptying, but does not significantly change C_{max} or AUC. The volume of distribution of naproxen is about 0.09-0.16 L/kg. The drug distributes into synovial fluid to reach about 50% of plasma levels 3-4 hr after dosing. Naproxen is ≥ 99% bound to plasma proteins (albumin), and this binding decreases with increasing plasma drug concentrations. Disproportional increments in naproxen AUC at doses > 500 mg/day are attributed to nonlinear plasma protein binding. Despite nonlinear disposition, the half-life of naproxen is independent of dosage or plasma concentration after both single or multiple doses; reported values are 12 - 16 hr. In humans, naproxen is metabolized to naproxen glucuronide (40%), an unknown conjugate (20%) and 6-desmethylnaproxen (28%). The latter moiety is itself conjugated with glucuronide (12%). Less than 10% of naproxen is excreted unchanged in the urine. About 95% of a dose appears in the urine after 5 days, with less than 5% fecal excretion.

The major adverse reaction is GI irritation, GI upset and dyspepsia, but serious GI toxicity (ulceration, bleeding, and perforation) can occur with chronic use.

Naproxen is currently marketed as Naprosyn^{R} (Syntex) as 250-, 375-, and 500-mg tablets (NDA #17581 approved 4/15/82), and as a 125 mg/5 mL suspension (NDA #18965 approved 3/23/87).

III. Study Details

A. Study under Fasting Conditions

1. Protocol # BABE 4065

2. Sponsor: Danbury Pharmacal
   Danbury, CT

3. Study sites:
   Clinical st

   Analytical:

4. Investigators:
   Principal investigator:

   Associate investigator:

   Study monitors:

   Loren Gelber, Ph.D.
   Danbury Pharmacal

5. Clinical study dates: March 9-30, 1991

6. Study design: Randomized, single dose, 3-treatment, 3-period, crossover study.

7. Dosing and product information: A single dose of 500 mg strength of either the test or reference product was administered orally at 0 hour with 240 mL of water after fasting for eight hours.

   (a) Test product #1:
   1 x 500 mg Naproxen Tablets manufactured by

   Lot # 93144-0100

   Assay: 102.8%

   Content uniformity: 103.2% (%CV=2.5)

   Batch size: tablets

   (b) Test product #2:
   1 x 500 mg Naproxen Tablets manufactured by Danbury.

   Lot # 04867C

   Assay: 100.8%

   Content uniformity: 98.8-103.4% (%CV=1.2)

   Batch size: tablets

(c) Reference product:

1 x 500 mg Naprosyn^{R} Tablets manufactured by Syntex.

Lot # 61659

Assay: 101.3%

Content uniformity: 101.3% (%CV=0.5%)

Expiration date: May/92

Pairwise comparisons were made among the three products:

(1)

(2) Danbury vs. Syntex

(3)

8. Subjects: Twenty-four subjects participated in the study. Subject #8 did not return for Periods #2 and 3 and was replaced by Subject #25. Twenty-four subjects completed three periods of the study.

The subjects were healthy male volunteers between 18-30 years of age and within 10% of the ideal body weight for height and body frame as described in the Metropolitan Life Insurance Bulletin, 1983. The subjects were judged to be in good health on the basis of physical examination, medical history, blood chemistry, hematology and urinalysis.

Criteria for exclusion from the study were: a history of chronic alcohol consumption or drug addiction; thyroid, gastrointestinal, hematopoietic, renal, hepatic, or cardiovascular disease, tuberculosis, epilepsy, asthma, nasal polyps, peptic ulcers or diabetes; a history of allergic response to naproxen, aspirin or any other nonsteroidal anti-inflammatory medication; unacceptable laboratory values.

Subjects were not allowed to take any drugs including OTC preparations, vitamins or antacids for two weeks prior to and during the study period. Subjects were instructed to refrain from alcohol, xanthine-containing foods or beverages for 48 hours prior to drug administration and throughout the sample collection period. Smoking was not permitted.

Subjects were not permitted to lie down for the first four hours following administration of the drug to assure proper stomach emptying.

9. Food and fluid intake: The subjects fasted for eight hours prior to and 4 hours after the drug administration. Doses were administered with 240 mL of water. Water was allowed ad lib until one hour prior to dosing and after the four hour after dosing. Standard meals were served four and ten hours following drug administration.

10. Washout period: One week

11. Blood samples: A 10 mL venous blood was collected in a 10-mL Vacutainer containing anticoagulant at 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 7, 12, 24, 36, 48 and 60 hours after dosing. Plasma was separated and promptly frozen.

12. Urine samples: No urine samples were collected.

13. Subject monitoring: All subjects were ambulatory or seated for four hours after dosing. Blood pressure and heart rate were measured prior to dosing and four hours after dosing.

14. Statistical analysis: SAS-GLM procedures were used on AUC_t, AUC_{inf}, C_{max}, T_{max}, K_{el}, $t_{1/2}$ and blood levels at each sampling points. The 90% confidence intervals (CI) were calculated for AUC_t, AUC_{inf} and C_{max}.

B. Study under Nonfasting Conditions

1. Protocol # BABE4063

2. Sponsor: Danbury Pharmacal
Danbury, CT

3. Study sites:
Clinical st

Analytical:

4. Investigators:

Principal investigator

Associate investigator

Study monitors:

Loren Gelber, Ph.D.
Danbury Pharmacal

5. Clinical study dates: March 9-23, 1991

6. Study design: Randomized, single dose, 3-treatment, 3-period, crossover study.

7. Dosing and product information: A single dose of 500 mg strength of either the test or reference product was administered orally at 0 hour with 240 mL of water after fasting for eight hours followed by the standardized breakfast.

(a) Test product #1:

1 x 500 mg Naproxen Tablets manufactured by

Lot # 93144-0100

Assay: 102.8%

Content uniformity: 103.2% (%CV=2.5)

Batch size:

(b) Test product #2:

1 x 500 mg Naproxen Tablets manufactured by Danbury.

Lot # 04867C

Assay: 100.8%

Content uniformity: 98.8-103.4% (%CV=1.2)

Batch size:

(c) Reference product:

1 x 500 mg Naprosyn® Tablets manufactured by Syntex.

Lot # 61659

Assay: 101.3%

Content uniformity: 101.3% (%CV=0.5%)

Expiration date: May/92

Pairwise comparisons were made among the three products:

(1)

(2) Danbury vs. Syntex

(3)

8. Subjects: Twelve subjects participated in the study. Twelve subjects completed three periods of the study.

The subjects were healthy male volunteers between 19-35 years of age and within 10% of the ideal body weight for height and body frame as described in the Metropolitan Life Insurance Bulletin, 1983. The subjects were judged to be in good health on the basis of physical examination, medical history, blood chemistry, hematology and urinalysis.

Criteria for exclusion from the study were: a history of chronic alcohol consumption or drug addiction; thyroid, gastrointestinal, hematopoietic, renal, hepatic, or cardiovascular disease, tuberculosis, epilepsy, asthma, nasal polyps, peptic ulcers or diabetes; a history of allergic response to naproxen, aspirin or any other nonsteroidal anti-inflammatory medication; unacceptable laboratory values.

Subjects were not allowed to take any drugs including OTC preparations, vitamins or antacids for two weeks prior to and during the study period. Subjects were instructed to refrain from alcohol, xanthine-containing foods or beverages for 48 hours prior to drug administration and throughout the sample collection period. Smoking was not permitted.

Subjects were not permitted to lie down for the first four hours following administration of the drug to assure proper stomach emptying.

9. Food and fluid intake: The subjects fasted overnight for at least eight hours prior to the standardized breakfast and dosing. Doses were administered with 240 mL of water. Water was allowed ad lib until one hour prior to dosing and after the four hour after dosing. Standard meals were served four and ten hours following drug administration.

10. Washout period: One week

11. Blood samples: A 10 mL venous blood was collected in a 10-mL Vacutainer containing anticoagulant at 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 7, 12, 24, 36, 48 and 60 hours after dosing. Plasma was separated and promptly frozen.

12. Urine samples: No urine samples were collected.

13. Subject monitoring: All subjects were ambulatory or seated for four hours after dosing. Blood pressure and heart rate were measured prior to dosing and four hours after dosing.

14. Statistical analysis: SAS-GLM procedures were used on AUC_t, AUC_{inf}, C_{max}, T_{max}, K_{el}, $t_{1/2}$ and blood levels at each sampling points. The 90% confidence intervals (CI) were calculated for AUC_t, AUC_{inf} and C_{max}.

IV. Validation of Assay Method for Plasma Samples

V. In Vivo Results with Statistical Analysis

A. Study under Fasting Conditions

Twenty-four volunteers were dosed in the first period and Subject #8 did not return for the second period of the study. Subject #25 replaced Subject #8 and successfully completed all three periods of the study. Subject #25 had its third period dosing a week later than the rest of the 23 subjects who completed all three periods of the study under the fasting conditions.

Only one adversary experience was observed during the study periods, which was possibly related to the study drug. Subject #19 experienced mild nausea and drowsiness for four hours. Review of vital sign measurements during the study and the exit physical examination data suggested no remarkable or unexpected events.

All 24 subjects were used in the statistical analysis and this approach was acceptable to the Division of Bioequivalence. The Division of Bioequivalence calculated statistics using 23 subjects excluding the Subject #25. It was found that the 90% confidence intervals were as tight as those calculated by Danbury with 24 subjects due to the small intra- and inter-subject variability. The firm did not use log-transformation in the analysis.

This review is based on Danbury's statistics with 24 subjects.

1. Mean plasma levels

The following data showed that the intersubject variability for two of the test and one reference products were rather low especially with the plasma levels obtained after the T_{max}, which was approximately 2 hours. The %CV ranged from 14 to 41. ANOVA tables also showed low estimation of the intrasubject variability for the

plasma levels obtained after T_{max}. The %CV ranged from 8 to 24. No statistically significant differences in plasma levels were observed at all sampling periods except for at 3 hours when the comparisons were made in Danbury-Syntex and at alpha=0.05.

Nine non-zero plasma levels were obtained at zero hour out of 72 measurements. Seven out of the nine samples showed plasma levels close to the detection limit of the assay method, which was Other two samples showed plasma levels of double the detection limit. These non-zero values were apparently caused by residual plasma levels from previous dosing. The magnitudes of the non-zero values are negligible.

No sequence effect was observed at all sampling points. No period effect was observed at all sampling points except at zero, 48 and 60 hours when the plasma levels were approximately one tenth of the C_{max} or below.

All three products tested showed broad peak of plasma levels stretching from 1.5 hours to 4 hours as shown in Table 3.

Table 3. Plasma Naproxen Levels under Fasting Conditions (mcg/mL)

Time hrs	Test #1 Lot #93144-0100 Mean (SD)	Test #2 Danbury Lot #04867C Mean (SD)	Reference Syntex Lot #61659 Mean (SD)
0	0.029 (0.78)	0.029 (1.105)	0.052 (0.110)
0.50	21.25 (21.4)	26.1 (24.4)	26.1 (27.6)
1.00	43.4 (29.6)	53.3 (27.2)	45.3 (29.3)
1.5	53.0 (25.6)	62.9 (23.5)	59.5 (27.2)
2.00	58.6 (24.3)	63.7 (18.3)	62.5 (19.2)
2.50	59.7 (21.7)	63.9 (13.6)	64.2 (14.8)
3.00	56.8 (16.4)	63.6 (9.07)	62.3 (14.8)
3.50	57.3 (14.4)	59.4 (8.21)	59.9 (9.92)
4.00	55.9 (11.3)	57.8 (7.74)	56.7 (10.4)
5.00	52.5 (11.1)	51.3 (7.61)	50.4 (8.22)
7.00	41.6 (8.67)	41.0 (6.21)	40.5 (6.20)
12.0	30.0 (5.68)	29.9 (4.55)	29.2 (3.98)
24.0	17.1 (3.35)	16.8 (3.18)	17.0 (2.97)
36.0	10.5 (2.74)	10.5 (2.74)	10.1 (2.17)
48.0	6.43 (2.08)	6.45 (1.93)	6.43 (1.63)
60.0	4.16 (1.36)	4.27 (1.36)	4.23 (1.19)

2. Pharmacokinetic parameters

The 90% confidence intervals for the AUC_t, AUC_{inf}, and C_{max} met the requirements of the 80-120% range as shown in Table 3 when the three products were compared in Danbury-Syntex and Due to the low variability in the plasma levels as mentioned earlier, the 90% confidence intervals for all the pharmacokinetic parameters were very tight as shown in Table 4. The test mean/reference mean ratios for the AUC_t, AUC_{inf}, and C_{max} were all within the range of 0.98-1.02.

No sequence and period effects were observed for the AUC_t, AUC_{inf}, and C_{max}.

Table 4. Pharmacokinetic Parameters for Naproxen under Fasting Conditions

Parameter	Test #1 Lot #93144-0100	Test #2 Danbury Lot #04867C	Reference Syntex Lot #61659
AUC_t mcg.hr/mL	1129	1144	1127
SD	(186)	(175)	(162)
T Mean/R Mean Ratio			
	--	0.987	1.00
Danbury	--	--	1.02
90% CI			
	--	97-101	98-102
Danbury	--	--	100-104
AUC_{inf} mcg.hr/mL	1233	1262	1234
SD	(220)	(215)	(192)
T Mean/R Mean Ratio			
	--	0.976	0.999
Danbury	--	--	1.02
90% CI			
	--	95-100	98-102
Danbury	--	--	100-105

Table 4. (Continued)

Parameter	Test #1 Lot #93144-0100	Test #2 Danbury Lot #04867C	Reference Syntex Lot #61659
C_{max} mcg/mL	77.00	77.3	77.7
SD	(10.7)	(11.4)	(11.8)
T Mean/R Mean Ratio			
	--	0.996	0.991
Danbury	--	--	0.994
90% CI			
	--	97-103	96-102
Danbury	--	--	96-102
T_{max} hrs	2.06	1.90	1.98
SD	(1.17)	(8.60)	(0.938)
T Mean/R Mean Ratio			
	--	1.09	1.04
Danbury	--	--	0.96
K_{el} hr^{-1}	0.042	0.040	0.041
SD	(0.005)	(0.008)	(0.005)
T Mean/R Mean Ratio			
	--	1.06	1.02
Danbury	--	--	0.969
$t_{1/2}$ hrs	16.7	18.5	17.1
SD	(1.83)	(5.59)	(1.96)
T Mean/R Mean Ratio			
	--	0.905	0.977
Danbury	--	--	1.08

B. Study under Nonfasting Conditions

Twelve volunteers participated in the study and completed all three periods of the study. Subject #8 experienced a headache during the washout period after the first dosing. One 200 mg tablet of ibuprofen was taken. This was not considered to be related to the study drug and the subject finished the study.

Review of vital sign measurements during the study and the exit physical examination data suggested no remarkable or unexpected events.

All 12 subjects were used in the statistical analysis. The firm did not use log-transformation in the analysis.

1. Mean plasma levels

The following data obtained under nonfasting condition also showed low intersubject and intrasubject variability among two of the test and one reference products especially with the plasma levels obtained after the T_{max} , which was approximately 3-4 hours. The magnitude of the variabilities were comparable between the fasting and nonfasting studies. Statistically significant differences in plasma levels were observed only at 4, 36 and 60 hours for and at 1, 1.5, 4 and 7 hours for Danbury-Syntex at alpha=0.05.

Three non-zero plasma levels were obtained at zero hour out of 36 measurements. One sample showed a plasma level close to the detection limit of the assay method, which was Other two samples showed plasma levels of double the detection limit. These non-zero values were apparently caused by residual plasma levels from previous dosing. The magnitudes of the non-zero values are negligible.

No sequence effect was observed at all sampling points. No period effect was observed at all sampling points except at 4 and 60 hours.

Table 5. Plasma Naproxen Levels under Nonfasting Conditions (mcg/mL)

Time hrs	Test #1 Lot #93144-0100 Mean (SD)	Test #2 Danbury Lot #04867C Mean (SD)	Reference Syntex Lot #61659 Mean (SD)
0	0.0(0.0)	0.0(0.1)	0.1(0.1)
0.5	14.3(22.6)	13.2(14.4)	3.6(5.4)
1.0	23.7(23.7)	29.3(23.6)	12.0(11.2)
1.5	35.7(25.3)	42.9(23.8)	25.9(13.5)
2.0	45.7(26.4)	51.7(21.6)	38.8(8.8)
2.5	49.0(20.8)	59.6(33.1)	46.4(8.3)
3.0	50.5(17.6)	50.8(16.4)	52.9(11.7)
3.5	49.5(15.4)	50.4(14.7)	53.7(10.0)
4.0	47.9(11.9)	48.8(11.1)	55.5(9.7)
5.0	53.6(10.0)	52.0(5.9)	54.5(5.5)
7.0	44.7(6.6)	41.1(5.4)	47.1(5.7)
12.0	34.6(6.0)	33.4(5.2)	34.9(5.6)
24.0	19.0(3.6)	18.8(3.7)	19.4(2.7)
36.0	11.0(2.5)	11.3(2.7)	12.0(2.6)
48.0	7.0(2.3)	6.9(2.0)	7.3(1.8
60.0	4.4(1.6)	4.6(1.4)	4.8(1.6)

2. Pharmacokinetic parameters

The test mean/reference mean ratios for the AUC_t, AUC_{inf}, C_{max}, T_{max}, and K_{el} met the requirements of the 0.8-1.20 range as shown in Table 6 when the three products were compared in Danbury-Syntex and Due to the low variability in the plasma levels as mentioned earlier, the 90% confidence intervals for the AUC_t and AUC_{inf} were within 80-120% range with only twelve subjects used in the study.

No sequence and period effects were observed for the AUC_t, AUC_{inf}, and C_{max}.

Table 6. Pharmacokinetic Parameters for Naproxen under Nonfasting Conditions

Parameter	Test #1 Lot #93144-0100	Test #2 Danbury Lot #04867C	Reference Syntex Lot #61659
AUC_t mcg.hr/mL	1171	1162	1193
SD	(141)	(123)	(144)
T Mean/R Mean Ratio			
	--	1.01	0.981
Danbury	--	--	0.974
AUC_{inf} mcg.hr/mL	1277	1276	1313
SD	(193)	(162)	(191)
T Mean/R Mean Ratio			
	--	1.00	0.973
Danbury	--	--	0.972
C_{max} mcg/mL	66.90	68.5	60.5
SD	(10.8)	(26.3)	(9.07)
T Mean/R Mean Ratio			
	--	0.977	1.11
Danbury	--	--	1.13
T_{max} hrs	3.83	3.08	4.13
SD	(3.03)	(1.47)	(1.30)
T Mean/R Mean Ratio			
	--	1.24	0.929
Danbury	--	--	0.747

Table 6. (Continued)

Parameter		Test #1 Lot #93144-0100	Test #2 Danbury Lot #04867C	Reference Syntex Lot #61659
K_{el} hr^{-1}		0.044	0.042	0.042
	SD	(0.006)	(0.004)	(0.006)
	T Mean/R Mean Ratio			
		--	1.04	1.04
	Danbury	--	--	0.998
$t_{1/2}$ hrs		16.1	16.7	16.8
	SD	(2.12)	(1.86)	(2.33)
	T Mean/R Mean Ratio			
		--	0.965	0.961
	Danbury	--	--	0.996

VI. Dissolution

A. Formula Comparison

Formula compositions for Danbury's 250 mg, 375 mg, and 500 mg tablets are summarized in Table 7. The products in three different strengths are proportionally similar in active and inactive ingredients.

Table 7. Formula Compositions

Ingredients	mg per Tablet 250 mg	375 mg	500 mg
Croscarmellose Sodium			
Green Lake Blend			
Purple Lake Blend			
Magnesium Stearate NF			
Naproxen USP			
Povidone USP			
Total Weight (mg)	267.66	401.5	535.32

B. Dissolution Testing

Comparative dissolution testing of Danbury's test products, test product and Syntex's reference products shows that Danbury's four test products met the FDA/USP dissolution specifications (NLT in 45 min; 900 mL of pH 7.4 phosphate buffer; USP XXII paddle, 50 rpm). Dissolution data are summarized in Table 8.

Assay and content uniformity data for the products used in the dissolution testing are summarized in Table 9.

VII. Comments

1. Study under fasting conditions:

Pairwise comparison was made in Danbury-Syntex and for the 3-treatment 3-period study. The bioequivalence study under fasting conditions demonstrated that the test products by and Danbury and the reference product by Syntex are bioequivalent.

The 90% confidence intervals for the AUC_t, AUC_{inf}, and C_{max} were all within the 80-120% range. The test mean/reference mean ratios for the AUC_t, AUC_{inf}, C_{max} and T_{max} were all within 0.96-1.09 range. No statistically significant differences in plasma levels were observed at all sampling time points except for at 3 hours when the comparisons were made in , Danbury-Syntex and at alpha=0.05. No sequence effect was observed at all sampling time points. No period effect was observed at all sampling time points except at zero, 48 and 60 hours when the plasma levels were approximately one tenth of the C_{max} or below.

2. Study under nonfasting conditions:

Pairwise comparison was made in , Danbury-Syntex and for the 3-treatment 3-period study. The bioequivalence study under nonfasting conditions demonstrated that the test products by and Danbury and the reference product by Syntex are bioequivalent.

The test mean/reference mean ratios for the AUC_t, AUC_{inf}, C_{max}, T_{max}, and K_{el} met the requirements of the 0.8-1.20. Plasma levels were comparable for the three products studied. Statistically significant differences in plasma levels were observed only at 4, 36 and 60 hours for and at 1, 1.5, 4 and 7 hours for Danbury-Syntex at alpha=0.05. No sequence and period effects were observed for the AUC_t, AUC_{inf}, and C_{max}.

3. The extent of absorption was similar under the fasting and nonfasting conditions for all the products tested. However, the rate of absorption appears to be slower under the nonfasting conditions. C_{max} was 11-13% lower under the nonfasting conditions than under the fasting conditions. T_{max} was 1-2 hours slower under the nonfasting conditions than under the fasting conditions.

4. Validation of assay method for naproxen: The specificity, sensitivity, linearity, precision, accuracy and recovery of the method are acceptable. Chemical stability of naproxen under storage and freeze-thaw cycles was acceptable.

5. The batch size for Danbury's test product used in the biostudy was tablets.

6. Adverse reactions: Only two mild adversary experiences were observed during the studies under fasting and nonfasting conditions. Subject #19 experienced mild nausea and drowsiness for four hours in the study under fasting conditions and Subject #8 experienced a headache during the washout period after the first dosing in the study under nonfasting conditions. No other serious adverse reactions were reported.

7. The dissolution data for the 250 mg, 375 mg and 500 mg strength tablets manufactured with naproxen met the FDA/USP specifications. The dissolution data for the 500 mg strength tablets manufactured with naproxen also met the FDA/USP specifications.

8. The firm demonstrated that the 250 mg and 375 mg tablets are proportionally similar in its active and inactive ingredients to the 500 mg tablet.

VIII. Deficiency

None.

IX. Recommendations

1. The two in vivo bioequivalence studies conducted under fasting and nonfasting conditions by Danbury Pharmacal on its Naproxen Tablets, 500 mg strength, lot #04867C, comparing it to Syntex's Naprosyn® Tablets, 500 mg strength, lot #61659, have been found acceptable. The studies demonstrate that Danbury's Naproxen Tablets, 500 mg strength, is bioequivalent to the reference product, Naprosyn® Tablets, 500 mg strength.

2. The dissolution testing conducted by Danbury on its Naproxen Tablets, 250 mg strength, lot #05066C, 375 mg strength, lot #05067C, and 500 mg strength, lot #04867C, is acceptable. The formulations for the 250 mg and 375 mg strengths tablets are proportionally similar to the 500 mg strength tablets of the test product which underwent two acceptable bioequivalence studies (submission date: 12/31/91). The waivers of in vivo bioequivalence study requirements for the 250 mg and 375 mg strengths of the test product are granted. The 250 mg and 375 mg strengths tablets of the test product are therefore deemed bioequivalent to Syntex's Naprosyn®, 250 mg and 375 mg tablets, respectively.

3. The dissolution testing conducted by Danbury on its Naproxen Tablets, 500 mg strength, lot #05587C, manufactured with naproxen raw material is acceptable. The formula of the test product manufactured with the alternate raw material is identical to the formula of the 500 mg strength tablets of the test product manufactured with naproxen raw material which underwent two acceptable bioequivalence studies (submission date: 12/31/91). Therefore, a waiver of the bioequivalence study requirements for the test product manufactured with naproxen is granted. The firm's test product manufactured with the alternate naproxen raw material manufactured by is, therefore, deemed bioequivalent to its test product manufactured with the naproxen raw material manufactured by

4. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of pH 7.4 Phosphate Buffer at 37°C using USP XXII Apparatus II (Paddle) at 50 rpm. The test product should meet the following specifications:

Not less than of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

The firm should be informed of the recommendations.

Moo Park, Ph.D.
Review Branch III
The Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRE _____ 3/25/92

Concur: _____ Date: 4/14/92
S.V.Dighe, Ph.D.
Director
Division of Bioequivalence

cc: ANDA #74-163, HFD-604(Hare), HFD-658 (Mhatre, Park), HFC-130/JAllen, Drug File

(Please type the input and press F9.)

Table 8. In Vitro Dissolution Testing

Drug (Generic Name):Naproxen Tablets
Dose Strength:250 mg, 375 mg and 500 mg
ANDA No.:74-163
Firm:Danbury Pharmacal
Submission Date:12/31/91
File Name:74163SDW.D91

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle:x RPM:50
No. Units Tested:12
Medium:pH 7.4 Phosphate Buffer Volume:900 mL
Specifications:NLT n 45 min
Reference Drug:Syntex's Naprosyn Tablets
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot #04867C(Danbury) Strength(mg)500			Reference Product Lot #61659(Syntex) Strength(mg)500		
	Mean %	Range	%CV	Mean %	Range	%CV
15	96.5		4.7	101.4		0.4
30	101		1.2	102.1		0.4
45	102		0.6	102.1		0.3

Sampling Times (Minutes)	Test Product Lot #05587C(Danbury) Strength(mg)500			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
15	100.0		2.0			
30	102.4		0.9			
45	102.8		1.4			

Sampling Times (Minutes)	Test Product Lot #93144-100 Strength(mg)500			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
15	88.7		2.7			
30	100.0		2.8			
45	103.4		3.3			

Sampling Times (Minutes)	Test Product Lot #05067C(Danbury) Strength(mg)375			Reference Product Lot #93255(Syntex) Strength(mg)375		
	Mean %	Range	%CV	Mean %	Range	%CV
15	98.6		2.3	99.4		2.2
30	100.9		1.8	100.7		1.3
45	100.7		1.4	101.0		1.0

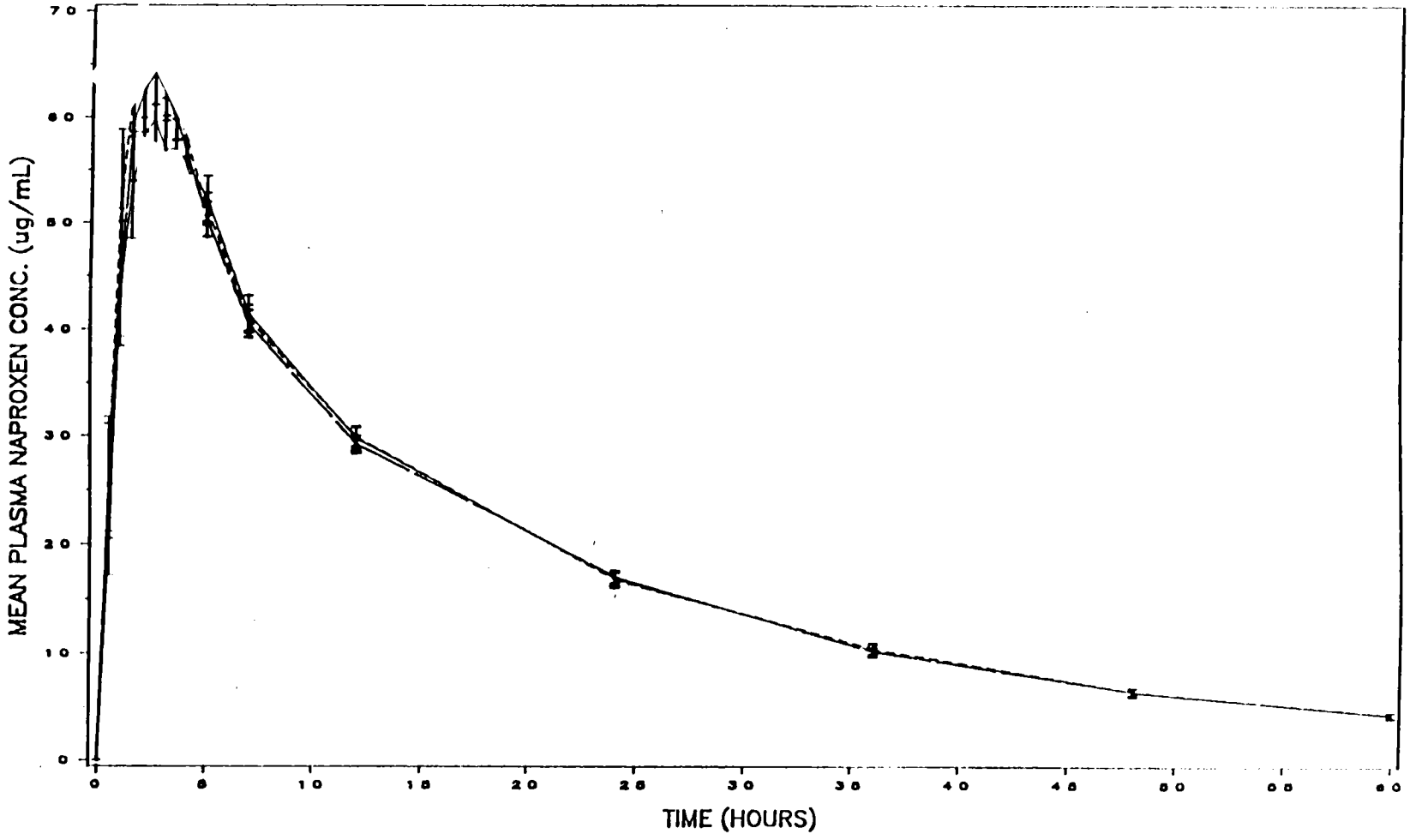
Sampling Times (Minutes)	Test Product Lot #05066C(Danbury) Strength(mg)250			Reference Product Lot #82986(Syntex) Strength(mg)250		
	Mean %	Range	%CV	Mean %	Range	%CV
15	99.5		2.3	101.0		0.7
30	101.2		1.4	101.5		1.2
45	101.3		1.4	101.5		1.2

Table 9. Assay and Content Uniformity Data

Product	Assay	Content Uniformity
Danbury's Naproxen 500 mg Tablet Lot #05587C	99.6%	102.8%(CV=1.7%)
Danbury's Naproxen 375 mg Tablet Lot #05067C	99.2%	100.2%(CV=1.9%)
Danbury's Naproxen 250 mg Tablet Lot #05066C	100.9%	100.4%(CV=1.9%)
Syntex's Naprosyn 375 mg Tablet Lot #93255	102.2%	100.5%(0.8%)
Syntex's Naprosyn 250 mg Tablet Lot #82986	101.0%	101.5%(CV=0.5%)

NAPROXEN IN HUMAN PLASMA
DANBURY PHARMACAL, INC.
MEAN (+/- SEM) PLASMA NAPROXEN CONCENTRATION
FIGURE 1

Fasting Study



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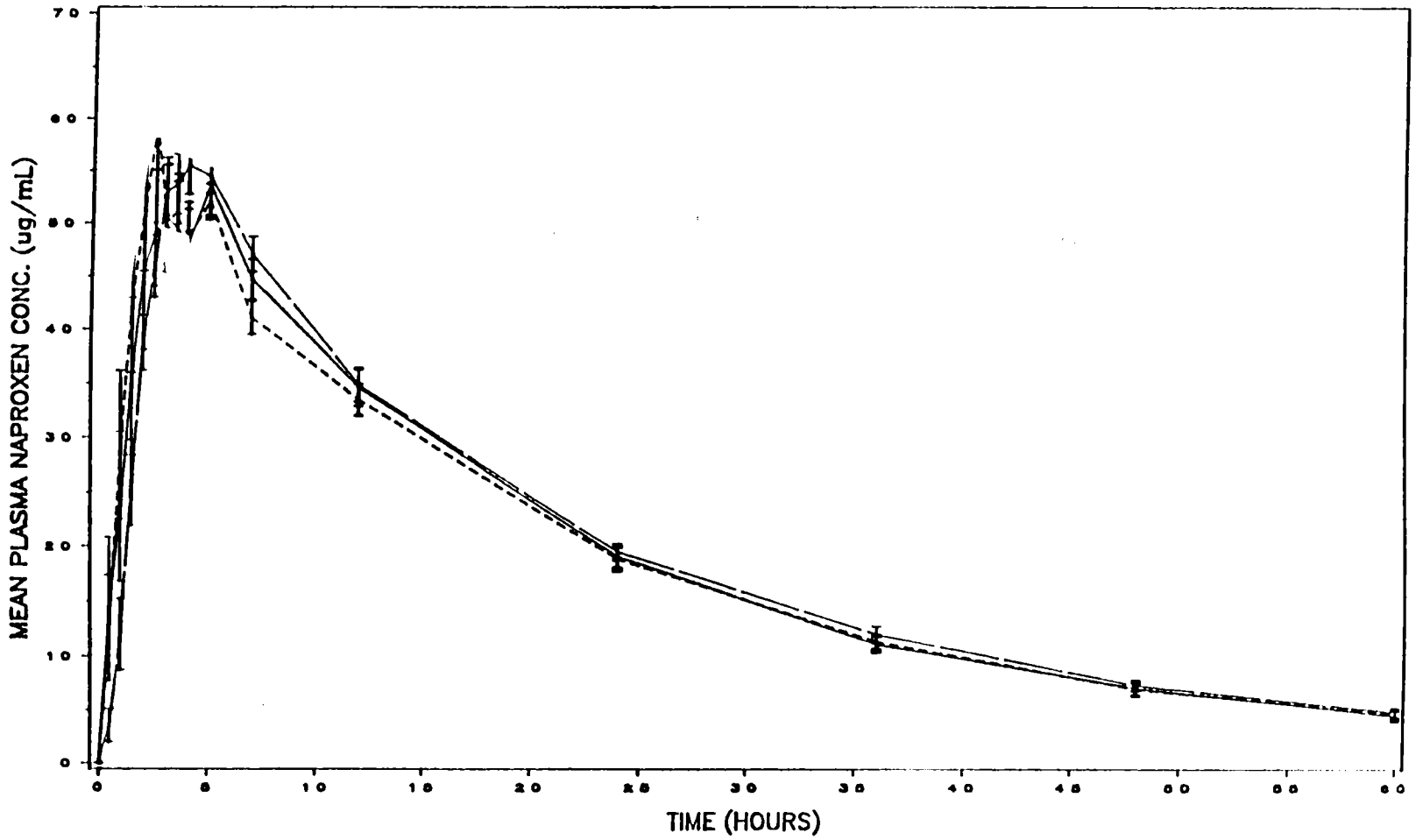
NAPROXEN IN HUMAN PLASMA
DANBURY PHARMACAL, INC.
MEAN (+/- SEM) PLASMA NAPROXEN CONCENTRATION
FIGURE 1

Food Study



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